Predicting and improving individual long-term outcome in patients with diabetes and nephropathy

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Determinants of response to RAAS inhibition

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Introduction and aims of the thesis

The burden of renal disease in patients with type 2 diabetes

The prevalence of type 2 diabetes has steadily increased during the last decades and become a major global health problem.[1] Patients suffering from diabetes are at increased risk for developing macrovascular and microvascular complications.[2] These complications have been associated with a reduced life expectancy. Renal microvascular complications, in particular those associated with diabetes, have led to an increased number of patients developing progressive renal function decline eventually resulting in end stage renal disease (ESRD).[3,4] Prevention of ESRD is of major importance as it is associated with a high risk of cardiovascular morbidity and mortality but places a substantial burden on patient's well being and health care expenditures.[5]

The introduction of RAAS blocking agents

In the holistic approach of diabetes, blood pressure reduction is of major importance to reduce the renal and cardiovascular risk.[6,7] When renal disease advances, patients use an increased number of several antihypertensive drugs to achieve an adaequate blood pressure goal necessary to reduce this renal and cardiovascular risk.

The introduction of the angiotensin converting enzyme (ACE) inhibitors, intervening in the Renin-Angiotensin-Aldosterone-System (RAAS) has led to new insights in the treatment of patients with diabetic nephropathy. In addition to blood pressure reduction, it was postulated that blockade of the RAAS also exerts local renal effects. By reducing glomerular pressure and protein leakage - both considered as risk factors for progressive renal function loss - ESRD could be prevented.[8,9]

ACE inhibitors were the first inhibitors of the RAAS to demonstrate renal protection beyond reduction of blood pressure as seen with conventional therapy. Firstly, enalapril was shown to confer renoprotection in patients with type 1 diabetes and nephropathy.[10] A couple of years later, this was confirmed by Lewis et al. in a trial with captopril in patients with type 1 diabetes and nephropathy.[11]

Angiotensin receptor blocking therapy in patients with diabetic nephropathy

Subsequently, a new class of drugs intervening in the RAAS system, the angiotensin receptor blockers (ARBs) showed similar results of renoprotection beyond that could be expected from blood pressure alone in patients with diabetes 2 and advanced renal disease. The renoprotective effect of ARBs was demonstrated in two landmark trials, the Reduction of Endpoints in non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials.[12,13] These included essentially similar patients with advanced stages of type 2 diabetes and nephropathy associated with overt proteinuria excretion.[14, 15] These trials demonstrated that ARB treatment, on top of existing antihypertensive treatment, was beneficial in slowing the progression to ESRD, and thus, in delaying the time to dialysis or renal transplantation.

However, despite the 28 percent and 23 percent reduction in the chance of developing

ESRD, as shown in the RENAAL and IDNT trials, respectively, patients were still at a high residual risk for renal and cardiovascular events of approximately 10% per year.[16] Although RAAS blockade is considered a cornerstone therapy in the treatment in patients with type 2 diabetes and nephropathy to reduce progressive renal function loss, apparently it cannot prevent the progression to ESRD in all patients. As patients treated with RAAS blocking agents still have a certain amount of residual risk for renal and cardiovascular morbidity and mortality, identification of novel strategies to enhance the protective effects of RAAS blocking intervention is much needed.

Scope of the thesis

In this thesis we aim to provide insights into novel ways of how the protective effects of RAAS inhibition with ARB therapy in patients with diabetes and nephropathy can be optimized.

Although this is the main focus, early identification of patients who are at increased risk of developing diabetic nephropathy, and subsequent renal and cardiovascular morbidity and mortality, is also considered of major importance to devise the most efficient treatment strategy for each individual. The cardiovascular risk of an individual patient has classically been based on traditional (Framingham) risk predictors by means of age, blood pressure, presence of diabetes, cigarette smoking, overweight, cholesterol level and family history of cardiovascular disease.[17] However, drugs may also exert effects on other renal risk factors that are not included in traditional risk scores. For example, ARBs reduce albuminuria or increase serum potassium that either may decrease long-term renal or cardiovascular risk (albuminuria) or increase this risk (serum potassium). Exploration of the influence of renal biomarkers to identify which patients benefit from therapy in the long-term could be very helpful in optimizing current 'state-of-the-art' therapy to improve long-term renal and cardiovascular protection for each individual. In Chapter two an introductory review is provided on the role of the renal risk markers glomerular filtration rate (GFR) and albuminuria for identifying patients at risk of developing diabetic nephropathy.

In the next chapters, the short-term effect of a drug, in particular an ARB, on risk factors that either influence long-term renal and cardiovascular risk in a positive or negative way is investigated. In Chapter three, the individual response on blood pressure and albuminuria is evaluated and the predictive value of these markers in reducing cardiovascular risk of patients with type 2 diabetes and nephropathy determined. In Chapter four the implication of a fall in eGFR during initiation of ARB treatment for the prediction of success of therapy is evaluated and explained from a pharmacological perspective. In Chapter five the initial change in serum potassium during ARB and calcium channel blocker therapy is investigated as well as its implication for long-term cardiovascular outcome. In addition to the short-term treatment effect on a risk marker, external factors may also influence the effect of a drug. In Chapter six it is studied whether the amount of dietary sodium intake during ARB therapy may influence the efficacy of this therapy to confer renal or cardiovascular protection. Finally, these chapters are summarized and discussed in Chapter seven. We hope that this information

on how to optimize ARB therapy in patients with diabetes and nephropathy will help to reduce the burden of renal and cardiovascular complications in this patient population.

References

1. Huang ES, Basu A, O'Grady M, Capretta JC. Projecting the future diabetes population size and related costs for the U.S. Diabetes Care. 2009 Dec;32:2225-9.

2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998 Jul 23;339:229-34.

3. Hallan SI, Coresh J, Astor BC, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2006 Aug;17:2275-84.

4. US renal data system: USRDS 2007 annual data report, bethesda, national institutes of health, national institute of diabetes and digestive and kidney diseases, available online: Http://www.usrds.org/adr.htm.

5. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004 Sep 23;351:1285-95.

6. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK prospective diabetes study group. BMJ. 1998 Sep 12;317:703-13.

7. Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. Lancet. 1983 May 28;1:1175-9.

8. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med. 1982 Sep 9;307:652-9.

9. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med. 1998 Nov 12;339:1448-56.

10. Bjorck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. BMJ. 1992 Feb 8;304:339-43.

11. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-

enzyme inhibition on diabetic nephropathy. the collaborative study group. N Engl J Med. 1993 Nov 11;329:1456-62.

12. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 Sep 20;345:861-9.

13. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 Sep 20;345:851-60.

14. Brenner BM, Cooper ME, de Zeeuw D, et al. The losartan renal protection study--rationale, study design and baseline characteristics of RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan). J Renin Angiotensin Aldosterone Syst. 2000 Dec;1:328-35.

15. Rodby RA, Rohde RD, Clarke WR, et al. The irbesartan type II diabetic nephropathy trial: Study design and baseline patient characteristics. for the collaborative study group. Nephrol Dial Transplant. 2000 Apr;15:487-97.

16. de Zeeuw D, Heerspink HJ, Gansevoort RJ, Bakker JL. How to improve renal outcome in diabetes and hypertension - the importance of early screening for and treatment of microalbuminuria. Europ Nephrol. 2009:13.

17. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Executive summary: Fourth joint task force of the european society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2007 Oct;28:2375-414.

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Monitoring kidney function and albuminuria in patients with diabetes

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Abstract

Diabetes is a major global health problem. Affected individuals are at high risk to develop renal and cardiovascular complications. Since both complications are potentially preventable, it is important to identify patients at risk as early as possible. Renal biomarkers, in particularly albuminuria and estimated glomerular filtration rate (eGFR) have shown their clinical usefulness on top of classical cardiovascular risk markers, such as glucose and blood pressure, in predicting the risk for renal and cardiovascular disease. In addition, the short-term treatment induced changes in these biomarkers can be used as a therapeutic prognostic marker that indicates the degree of long-term risk reduction. This review highlights the importance of renal biomarkers (albuminuria and eGFR) and the changes in these biomarkers as predictors of renal and cardiovascular disease.

Keywords

Albuminuria, Glomerular filtration rate, Renal disease, Cardiovascular disease

Introduction

It is beyond doubt that patients with diabetes experience a high risk to develop renal and cardiovascular disease. Both outcomes have significant clinical implications and are associated with high additional costs. Several traditional (blood pressure, HbA1c, cholesterol) and novel cardiovascular biomarkers (C-reactive protein, pro-BNP) are at hand to identify those individuals that will develop end stage renal or cardiovascular disease, as early as possible. The traditional biomarkers have been successfully applied in clinical practice and have proven their clinical usefulness. Renal biomarkers, in particularly albuminuria and estimated glomerular filtration rate (eGFR), have been added to the biomarker armamentarium. Both are indeed associated with renal and cardiovascular disease in individuals with diabetes and may be used to identify those at risk for long-term complications. While identifying individuals at risk is important, even more important is the question whether we can lower this risk by changing renal biomarkers through pharmacological (or other) intervention. This overview describes the performance of albuminuria and eGFR in predicting renal and cardiovascular disease. In the second part the relationship between treatment induced changes in these two renal biomarkers and renal and cardiovascular outcome will be described.

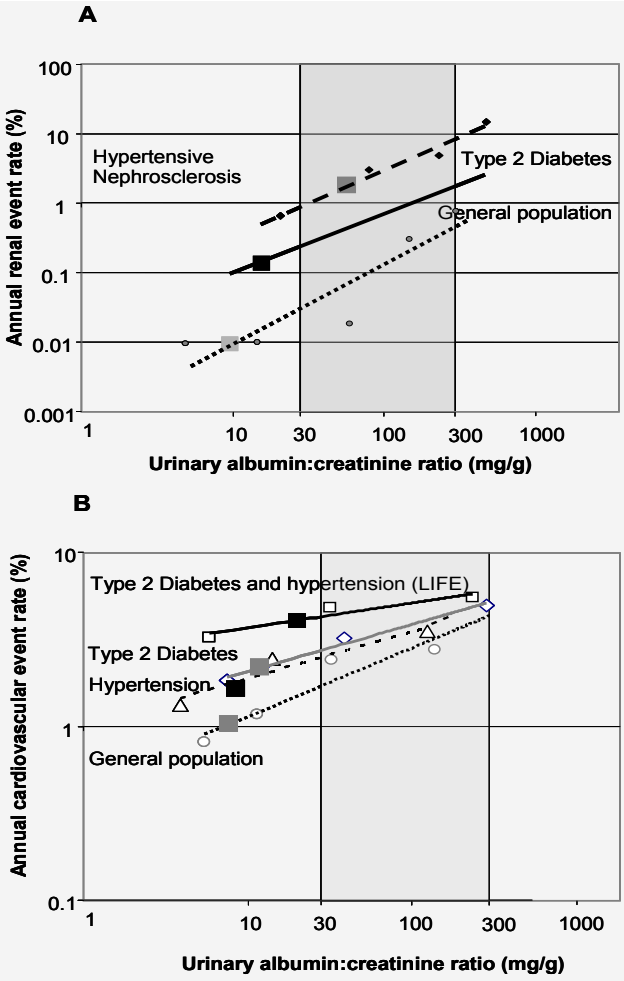

Figure 1A: Association between albuminuria level and the risk for renal outcomes in different populations. Data show the risk for ESRD for the general population (PREVEND), individiduals with type 2 diabetes (ADVANCE), and individuals with hypertensive nephrosclerosis (AASK). The protein:creatinine ratio, measured in the AASK trial, was converted to albumin:creatinine ratio. The center of the squares is placed on the average albuminuria level in each population.[6]

Figure 1B: Associations between albuminuria level and the risk for cardiovascular outcomes in different populations. Data show the risk for cardiovascular event in the type 2 diabetic population (ADVANCE), hypertensive population (LIFE), and general population (PREVEND). The center of the squares is placed on the average albuminuria level in each population.

Albuminuria and eGFR as predictors for renal and cardiovascular disease

Albuminuria

The relationship between albuminuria and renal and cardiovascular disease has been well established. Its association was first described in patients with type 1 diabetes.[1, 2] Several studies followed these initial reports and confirmed the significance of albuminuria in predicting long-term renal prognosis. Data from prospective trials showed that patients with type 2 diabetes appear to progress from micro- to macroalbuminuria to End Stage Renal Disease (ESRD) very similarly as the earlier reports of patients with type 1 diabetes. The Reduction in Endpoints in Non-Insulin Dependent Diabetes Mellitus.With the Angiotensin II Antagonist Losartan (RENAAL) showed that albuminuria is the most critical baseline predictor for end stage renal disease.[3] Similar data were observed in type 2 diabetic patients participating in the Irbesartan Diabetic Nephropathy Trial (IDNT).[4] A recent study provides further evidence of the importance of albuminuria as renal risk predictor in type 2 diabetes. Lorenzo et al. illustrate that the rate of renal function loss was higher in diabetic compared to non-diabetic patients.[5] Interestingly, after adjustment for the difference in albuminuria in the two patients groups the difference in eGFR decline was annihilated. These data confirm that patients with diabetes show faster renal function decline, but this is explained, at least to a large extent, by the higher levels of albuminuria. Prospective studies in different populations have shown that increased albuminuria is associated with increased renal risk (Figure 1A).[6]

After the discovery of increased albuminuria as renal risk marker, it soon became clear that increased albuminuria predicts cardiovascular disease as well. In patients with and without diabetes participating in the Heart Outcomes Prevention Evaluation (HOPE) trial, the presence of microalbuminuria was independently associated with increased risk for cardiovascular disease and mortality.[7] In a prospective study of subjects with type 2 diabetes, it was shown that those with microalbuminuria had a 1.8-fold increased risk for cardiovascular mortality during 12-years of follow-up compared to individuals with normoalbuminuria.[8] Because of these studies, microalbuminuria was evidently associated with CV and renal risk in diabetes. However, in the nineties studies followed demonstrating that the predictive capacity of microalbuminuria goes beyond diabetes. Prospective cohort studies in hypertensive individuals and in the general population showed that increased albuminuria is associated with increased cardiovascular risk (figure 1B). Interestingly, the slope of relation between albuminuria and renal and cardiovascular risk is similar in different populations and disease conditions, albeit at a different risk level.

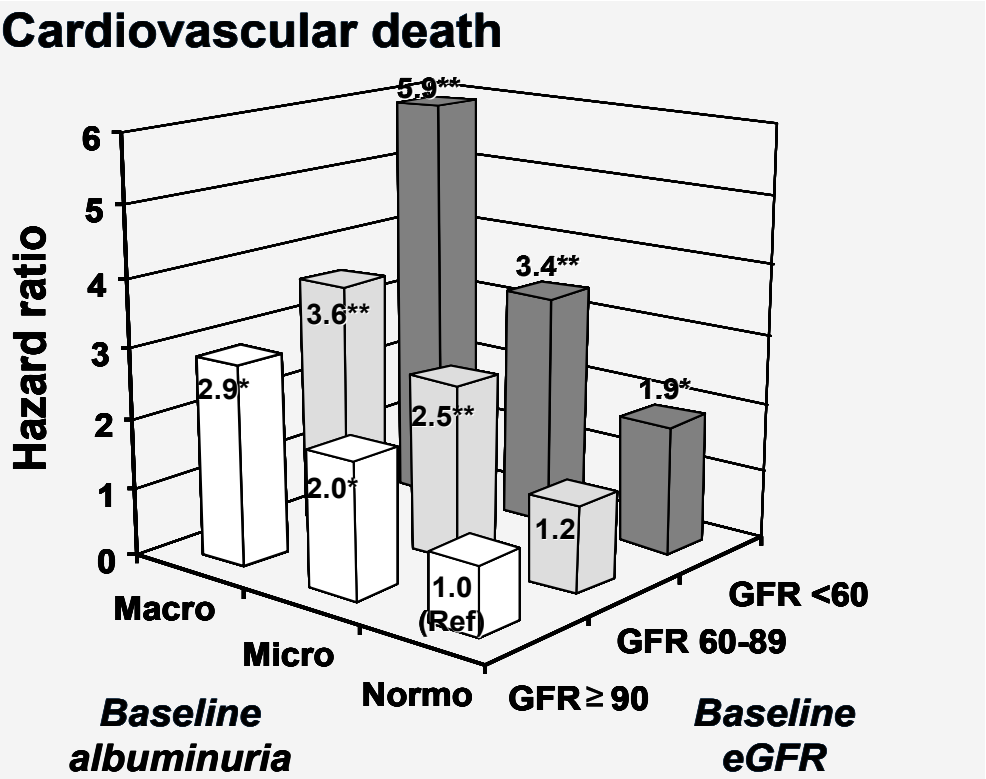

Figure 2: Combined effects of albuminuria and eGFR levels at baseline on the risk for adverse outcomes. The estimates are adjusted for baseline covariates, including age, gender, duration of diabetes, SBP, history of currently treated hypertension, history of macrovascular disease, HbA1c, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, BMI, electrocardiogram abnormalities, current smoking, and current drinking. Adapted with permission from T. Ninomiya et.al..[13]

Glomerular Filtration Rate

Although the best measure for GFR is obtained by techniques that involve infusing of exogenous substances, GFR is usually estimated in clinical practice by various formulae based on serum creatinine concentration, since this is much less invasive and time consuming. Serum creatinine is however affected also by factors other than glomerular filtration such as diet, muscle mass and tubular secretion.[9] To circumvent these limitations several equations have been developed to estimate GFR from serum creatinine concentration. The most popular equation nowadays used is the Modification of Diet in Renal Disease (MDRD) equation.[10]

It is known that next to albuminuria, a reduction in estimated GFR (eGFR) is also associated with a higher risk to develop end stage renal or cardiovascular disease. As early as 1989 minor increases in serum creatinine (reduction in eGFR) was found to predict mortality.[11] This study included 10,940 hypertensive individuals and demonstrated that those with a serum creatinine above 1.7 mg/dL had a more than 3-fold increased risk for 8-year mortality. Minor reductions in eGFR are linked to increased risk for renal and cardiovascular disease in patients with diabetes as well. Keane et.al. demonstrated that baseline serum creatinine was among the strongest risk predictors for ESRD in patients with type 2 diabetes and nephropathy.[12] The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial enrolled a broad range of type 2 diabetic patients with different degrees of renal impairment. In this population, every halving of eGFR measured at start of the trial was associated with a 1.5-fold and 1.9-fold increased risk for cardiovascular disease and cardiovascular death, respectively.[13] These effects were independent of other baseline renal/cardiovascular risk markers, including albuminuria. Interestingly, the combined effects of baseline albuminuria and eGFR for cardiovascular events and cardiovascular death were independent of each other (figure 2). The finding that albuminuria and eGFR are independent additive risk markers was recently confirmed in older adults with diabetes in the Cardiovascular Health study.[14] This study illustrated that both an increase in albuminuria and a reduction in eGFR almost doubled the risk for all-cause mortality compared to individuals with either a reduction in eGFR or elevation in albuminuria. The large proportion of patients with impaired eGFR but normal albuminuria, 62% in the ADVANCE trial and 53% in the Cardiovascular Health study, in addition to the data that each marker of kidney disease independently predicts renal or cardiovascular risk, further supports the concept that both eGFR and albuminuria are independent but complimentary manifestations of different pathology that is associated with CV risk. Albuminuria may reflect a certain disease state of the microvasculature (endothelial dysfunction), whereas a decrease in GFR may reflect activation of certain hormonal systems, such as the Renin-Angiotensin-Aldosterone-System (RAAS), in order to maintain GFR at an adequate level. These data provide an alternative concept to the traditional paradigm describing albuminuria and eGFR as serial manifestations of kidney disease whereby albuminuria precedes the decline in GFR. The independent additive value of albuminuria and eGFR supports guideline recommendations advocating the regular measurement of both albuminuria and eGFR to early identify patients at risk for renal and

cardiovascular complications.[15]

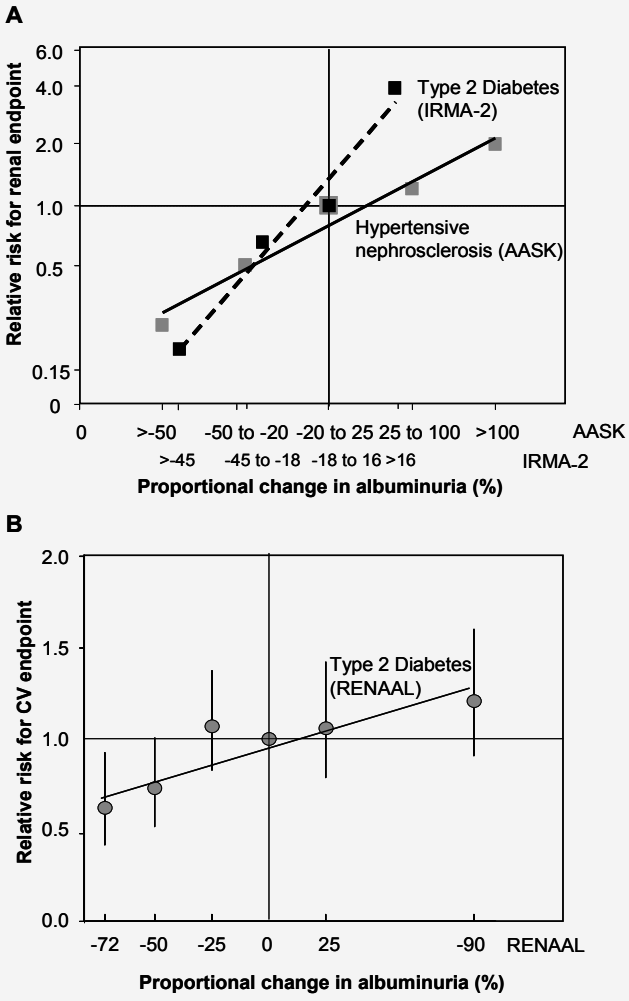

Figure 3A: Associations between the proportional change in albuminuria and the risk for renal outcomes. Renal endpoint in the IRMA-2 trial is diabetic nephropathy. The renal endpoint in the AASK trial is ESRD. The two x-axes indicate the ranges of albuminuria reduction for the two different individual trials.[6]

Figure 3B: Associations between the proportional change in albuminuria and the risk for cardiovascular outcomes in the type 2 diabetic population (RENAAL). Adapted with permission from de Zeeuw et al. [18]

Treatment induced changes in albuminuria or eGFR and association with renal and cardiovascular protection

Albuminuria and eGFR are useful biomarkers in predicting the risk for renal and cardiovascular events. However, to have any meaning in clinical practice, it is necessary to show that short-term treatment induced reductions in albuminuria or changes in eGFR are associated with long-term renal and cardiovascular protection.

Albuminuria

Several studies found that the extent of albuminuria reduction by inhibition of the RAAS has been associated with renal protection. In advanced diabetes and nephropathy, each 50% decrease in albuminuria during the first 6 months, induced by treatment with the angiotensin receptor blocker (ARB) losartan, was associated with a 45% decrease in the long-term risk for ESRD.[3] In patients with type 2 diabetes and early stage of nephropathy, the short-term reduction in albuminuria was also associated with a lower risk for renal disease progression (figure 3A).[6] Of note, these data extend to other populations, such as those with hypertension, as well (figure 3A).

Reductions in albuminuria are also linked with cardiovascular protection. Data from the Addenbrooke's hospital showed that patients with type 1 diabetes having a reduction or stable albuminuria during the first year of follow-up had a 48% reduction in their 5 years risk for cardiovascular disease compared to individuals with an increase > 30% in the first year.[16] A post-hoc analysis of the diabetic individuals in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial showed that the more the ARB losartan reduced albuminuria the better the long-term cardiovascular prognosis.[17] Similarly, every halving of albuminuria during follow-up in the ADVANCE trial was associated with a 20% reduction in the risk for cardiovascular events. This relationship was independent for the level of systolic blood pressure during follow-up and was, interestingly, comparable to the 18% cardiovascular risk reduction for every halving of albuminuria reported in the RENAAL trial (figure 3B).[13,18] These studies enrolled a large proportion of individuals with hypertension leaving the possibility that blood pressure reductions were the driving parameter for cardiovascular protection rather than albuminuria reduction (despite similar follow-up blood pressure levels in the treatment and control arm). An interesting small study in normotensive patients with type 2 diabetes and microalbuminuria showed that sustained reduction in albuminuria, with no changes or even rises in blood pressure, reflected reductions in the risk for cardiovascular complications.[19] This study provides further evidence that albuminuria can be regarded as an independent treatment goal for renal and cardiovascular protection. It must be remembered off course that these studies are all post-hoc analyses of randomized controlled trials. Prospective evidence that albuminuria reductions in itself are associated with cardiovascular protection are only small and performed in non-diabetic patients.[20] In diabetes such large studies are needed to resolve the issue whether specific lowering of albuminuria results in cardiovascular protection.

Although RAAS intervention (RAASi) is clearly beneficial in reducing albuminuria and delaying the progression of renal and cardiovascular disease, the optimal renal/cardioprotective dose of ACEIs and ARBs with respect to albuminuria lowering needs to be established.[21] Studies have shown that the use of high doses of ARBs, beyond going maximal recommended doses for blood pressure reduction, further lower albuminuria and may provide greater renal and cardiovascular benefit.[22, 23] However, long-term renal/cardiovascular outcome studies are required to assess the long-term efficacy and safety of exposure to such high doses.

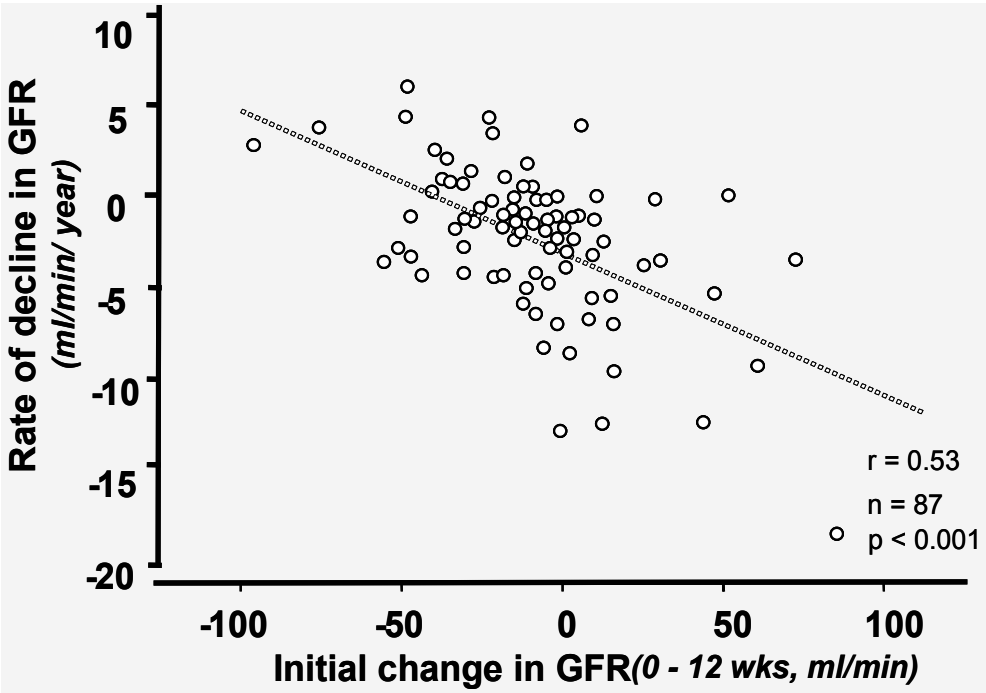

Figure 4: Acute fall in eGFR associated with slower rate of long-term renal function decline.

Glomerular Filtration Rate

Upon start of treatment with RAASi an acute rise in serum creatinine or drop in (e)GFR is noticed. This has led to inappropriate safety concerns, particularly among cardiologist, and underutilization of RAASi despite their proven benefit in clinical trials. In fact, the acute fall in eGFR upon starting RAASi is not a sign of worsening renal function, but has been associated with long-term renoprotection and can be used as a marker of therapeutic response. How to explain this, at first sight perhaps counterintuitive relationship? One should first realize that the acute fall in GFR upon RAASi initiation is of (reversible) hemodynamic origin owing to a reduction of intra-glomerular pressure rather than a treatment induced damage to functioning nephrons. Because of this reversible hemodynamic origin, treatment withdrawal leads to an increase in GFR of the same magnitude as the initial fall.

A couple of studies demonstrated that after withdrawal of antihypertensive therapy, the GFR increased in the majority of patients and correlated with the initial GFR fall.[24,25] Secondly, an increase in intra-glomerular pressure has been associated with progressive renal function decline.[26] This suggests that it may be possible that the degree of acute GFR fall (as measure of reduction in intra-glomerular pressure) is associated with renal and possibly cardiovascular protection. Indeed, Apperloo et al. demonstrated that the reversible reduction in GFR after start with ACE-inhibitor therapy was highly variable between patients. Interestingly, those patients with a greater initial fall in GFR had a significant less steep GFR slope during long-term follow-up (figure 4). Similar associations between an ACE-inhibitor induced acute eGFR fall and long-term renal prognosis were observed in post myocardial infarction (MI) patients.[27] Treatment with captopril caused a distinct fall during the first 3 days following a MI but remained stable during the 1 year follow-up. In contrast, the initial 3-days fall in GFR during placebo was less marked and continued to decline during the 1 year follow-up resulting in an overall 1 year GFR decline of 5.5 ml/min versus only 0.5 ml/min in the captopril group. Bakris and Weir reported a systematic review of 12 randomized trials (5 of them included solely patients with diabetes) and demonstrated that while GFR may be reduced acutely during ACE-inhibitor therapy, long-term renal function decline is markedly blunted compared to control treatment.[28] Thus, a fall in eGFR after start of RAASi can be interpreted as a marker of therapy responsiveness. This should consequently be taken as an encouragement to continue treatment, as long as other causes contributing to the fall in eGFR such as renal artery stenosis or diminished arterial blood volume or safety issues such as hyperkalemia can be excluded.

Conclusions

The renal biomarkers albuminuria and eGFR predict renal and cardiovascular complications in patients with diabetes beyond the set of classical cardiovascular biomarkers. The short-term (treatment induced) changes in albuminuria and eGFR indicate the long-term changes in renal and cardiovascular risk. This feature provides further clinical usefulness to these biomarkers.

References

1. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet. 1982 Jun 26;1:1430-2.

2. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med. 1984 Jul 12;311:89-93.

3. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. Kidney Int. 2004 Jun;65:2309-20.

4. Atkins RC, Briganti EM, Lewis JB, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis. 2005 Feb;45:281-7.

5. Lorenzo V, Saracho R, Zamora J, Rufino M, Torres A. Similar renal decline in diabetic and non-diabetic patients with comparable levels of albuminuria. Nephrol Dial Transplant. 2010 Mar;25:835-41.

6. Lambers Heerspink HJ, de Zeeuw D. Debate: PRO position. should microalbuminuria ever be considered as a renal endpoint in any clinical trial? Am J Nephrol. 2010;31:458,61; discussion 468.

7. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001 Jul 25;286:421-6.

8. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med. 2000 Apr 24;160:1093-100.

9. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med. 2006 Jun 8;354:2473-83.

10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. modification of diet in renal disease study group. Ann Intern Med. 1999 03/16;130:461-70.

11. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. results from the hypertension detection and

follow-up program. the hypertension detection and follow-up program cooperative group. Hypertension. 1989 May;13:I80-93.

12. Keane WF, Brenner BM, de Zeeuw D, et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL study. Kidney Int. 2003 Apr;63:1499-507.

13. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009 Aug;20:1813-21.

14. de Boer IH, Katz R, Cao JJ, et al. Cystatin C, albuminuria, and mortality among older adults with diabetes. Diabetes Care. 2009 Oct;32:1833-8.

15. Executive summary: Standards of medical care in diabetes--2010. Diabetes Care. 2010 Jan;33 Suppl 1:S4-10.

16. Yuyun MF, Dinneen SF, Edwards OM, Wood E, Wareham NJ. Absolute level and rate of change of albuminuria over 1 year independently predict mortality and cardiovascular events in patients with diabetic nephropathy. Diabet Med. 2003 Apr;20:277-82.

17. Ibsen H, Olsen MH, Wachtell K, et al. Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? the LIFE study. Diabetes Care. 2006 Mar;29:595-600.

18. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004 Aug 24;110:921-7.

19. Zandbergen AA, Vogt L, de Zeeuw D, et al. Change in albuminuria is predictive of cardiovascular outcome in normotensive patients with type 2 diabetes and microalbuminuria. Diabetes Care. 2007 Dec;30:3119-21.

20. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004 Nov 2;110:2809-16.

21. Heerspink HL, de Zeeuw D. Pharmacology: Defining the optimal dose of a new drug: A crucial decision. Nat Rev Nephrol. 2009 Sep;5:498-500.

22. Burgess E, Muirhead N, Rene de Cotret P, et al. Supramaximal dose of candesartan in proteinuric renal disease. J Am Soc Nephrol. 2009 Apr;20:893-900.

23. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Int. 2005 Sep;68:1190-8.

24. Apperloo AJ, de ZD, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney Int. 1997 03;51:793-7.

25. Hansen HP, Rossing P, Tarnow L, Nielsen FS, Jensen BR, Parving HH. Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. Kidney Int. 1995 06;47:1726-31.

26. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. J Clin Invest. 1985 Aug;76:612-9.

27. Hillege HL, van Gilst WH, van Veldhuisen DJ, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: The CATS randomized trial. Eur Heart J. 2003 03;24:412-20.

28. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Arch Intern Med. 2000 03/13;160:685-93.

3

Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: A post-hoc analysis of the combined RENAAL and IDNT trials

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Abstract

The long-term cardioprotective effect of angiotensin receptor blockers (ARBs) is associated with the short-term lowering of its primary target blood pressure, but also with the lowering of albuminuria. Since the individual blood pressure and albuminuria response to an ARB varies between and within an individual, we tested whether the variability and discordance in systolic blood pressure (SBP) and albuminuria response to ARB therapy is associated with its long-term effect on cardiovascular outcomes.

The combined data of the RENAAL and IDNT trials was used. We first investigated the extent of variability and discordance in SBP and albuminuria response (baseline to 6 months). Subsequently we assessed the combined impact of residual month 6 SBP and albuminuria level with cardiovascular outcome.

In ARB treated patients 421 patients (34.5%) either had a reduction in SBP but no reduction in albuminuria or vice versa, indicating substantial discordance in response in these parameters. The initial reduction in SBP and albuminuria independently correlated with cardiovascular protection: HR per 5 mmHg SBP reduction 0.97 (95% CI 0.94 – 0.99) and HR per decrement log albuminuria 0.87 (95% CI 0.76 – 0.99). Across all SBP categories at month 6, a progressively lower cardiovascular risk was observed with a lower albuminuria level. This was particularly evident in patients who reached the guideline recommended SBP target of ≤ 130 mmHg. The SBP and albuminuria response to ARB therapy is variable and discordant. Therapies intervening in the Renin-Angiotensin-Aldosterone-System with the aim to improve cardiovascular outcomes may therefore require a dual approach targeting both blood pressure and albuminuria.

Keywords

Diabetic nephropathy, Albuminuria, Blood pressure, Angiotensin receptor blocker, Cardiovascular disease

Introduction

Albuminuria and blood pressure are both cardiovascular risk markers in patients with diabetes and nephropathy.[1] Agents intervening in the Renin-Angiotensin-Aldosterone-System (RAAS) lower blood pressure and albuminuria and have been shown to be cardioprotective.[2,3] As RAAS inhibitors are introduced as antihypertensive agents, current guidelines recommend to titrate these drugs towards the maximum blood pressure lowering dose. It is assumed that such a blood pressure driven treatment strategy is paralleled by a reduction in albuminuria. However, two studies illustrate that both blood pressure and albuminuria responses are variable between individuals, and in addition that within an individual a blood pressure response is not always accompanied by a response in albuminuria and vice versa.[4,5] Both the lowering of blood pressure as well as the lowering of albuminuria have been independently associated with improved cardiovascular protection.[6,7] Based on this disparity in blood pressure and albuminuria response between and within an individual, one may argue that an approach focused solely on blood pressure reduction may not be the optimal strategy to confer cardiovascular protection.

To answer the question whether a treatment strategy that is concurrently aimed at reducing blood pressure and albuminuria would enhance the cardioprotective profile of RAAS intervention, we performed a post-hoc analysis of the combined data of the Reduction of Endpoints in NIDDM with the AII Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials, dealing with patients with type 2 diabetes and reduced kidney function. We first assessed the short-term response in blood pressure and albuminuria between and within individuals. We subsequently investigated whether reductions in blood pressure and albuminuria are independently associated with cardiovascular protection. Finally, we tested whether the achieved levels of blood pressure and albuminuria are independently associated with improved cardiovascular outcomes.

Methods

DIAMETRIC database

We conducted a retrospective analysis of the DIAMETRIC database. The database was established in 2009 and is comprised of 3228 adult patients with type 2 diabetes and nephropathy participating in the RENAAL and IDNT trials. The detailed design, rationale, and study outcome for these trials have been previously published.[8-11] Both trials investigated the efficacy of an ARB (irbesartan in IDNT, losartan in RENAAL) on renal outcomes in subjects with type 2 diabetes and nephropathy. In addition, the IDNT trial included a calcium antagonist (amlodipine) treatment arm. For the purpose of analysis we combined the calcium antagonist group with the placebo group of both trials. Inclusion criteria were similar but there were minor differences in detail for these trials. Patients with type 2 diabetes, hypertension and nephropathy aged between 30-70 years were eligible for these trials. Serum creatinine levels ranged between 1.0 mg/dL and 3.0 mg/dL. All subjects had proteinuria, defined as 24 hour urinary protein excretion of >900 mg in the IDNT trial whereas for RENAAL patients a urinary albumin to creatinine ratio (UACR) of >300 mg/g or a 24 hour urinary protein excretion >500mg/day was required. A 24 hour urinary albumin to creatinine ratio was calculated from the urinary albuminuria and creatinine data collected in IDNT. Exclusion criteria for both trials were type 1 diabetes or non-diabetic renal disease.

Patients randomized to study treatment were stepwise uptitrated in two periods of 4 weeks to achieve blood pressure target of at least 135/85 mmHg (50 to 100 mg losartan (RENAAL), 75 to 150 mg irbesartan (IDNT), or 2.5 to 10 mg amlodipine (IDNT)). After the end of the titration period, the dosage of other antihypertensive drugs were increased or additional antihypertensive agents (but not angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) in RENAAL and ACEis, ARBs, or calcium antagonists in IDNT) were added to achieve the target blood pressure.

The primary endpoint in each trial was essentially identical, consisting of the time to first event of doubling baseline serum creatinine, End Stage Renal Disease, or death. Cardiovascular outcomes were also collected in both trials. The cardiovascular outcome for this study was the composite of myocardial infarction, stroke, hospitalization for heart failure, or cardiovascular death. All cardiovascular outcomes were adjudicated by an independent blinded endpoint committee using rigorous outcome definitions. All cardiovascular events were included in the analysis instead of limiting the analysis to events that occurred after 6 months. To establish the validity of this approach a sensitivity analysis was conducted excluding the events that occurred during the first 6 months.

Blood pressure and albuminuria measurements

This post-hoc analysis focuses on the blood pressure and albuminuria (defined as the albumin to creatinine ratio) response from baseline to month 6. Blood pressure and albuminuria was measured in both the RENAAL and IDNT trials at baseline, month 3, and month 6. Patients included in this analysis were required to have their blood pressure measurement and collection of urine for albuminuria assessment not more than one day apart in order to obtain matched blood pressure and albuminuria values at baseline and month 6. Systolic blood pressure response was defined as the difference between the month 6 and baseline value. Albuminuria response at month 6 for each patient was calculated as (1 – ratio of month 6 to baseline albuminuria) multiplied by 100%. On the basis of previous analyses, the month 6 value was chosen because most parameters were measured at month 6, the treatment effects were considered fully present, and few events occurred during the first 6 months. All patients originally randomized to treatment were considered in this analysis. If participants had missing blood pressure and/or albuminuria values at month 6, the missing value was replaced by the last post-randomization value.

Statistical analyses

The changes in systolic blood pressure and albuminuria were stratified in four categories: <-15 mmHg; -15 – 0 mmHg; 0 – 15 mmHg; ≥ 15 mmHg change in systolic blood pressure and < -30; -30 – 0; 0 – 30; ≥30% change in albuminuria. A multivariate Cox model was used to assess the relationship between the magnitude of systolic blood pressure and albuminuria change and risk for cardiovascular outcomes. For exploration of the hazard ratio (HR) profile, HRs (95% CI) for participants according to quartiles in systolic blood pressure and log transformed albuminuria change was calculated. The variance of each quartile of systolic blood pressure and albuminuria change was calculated by using the absolute floating risk method.[12] The regression line for the risk estimates according to quintiles of month 6 change in systolic blood pressure and albuminuria was fitted using inverse variance weighting. Risk reductions per decrement log albuminuria are in the text described as percentage reduction ([1–hazard ratio]×100%). The multivariate Cox model included the following baseline covariates: age, gender, race, cardiovascular disease history, albuminuria, blood pressure lowering medication (a-blocker, β-blocker, calcium antagonist, diuretics), seated systolic and diastolic blood pressure, estimated glomerular filtration rate, HbA1c, cholesterol, weight, smoking as well as the month 6 change in albuminuria, seated systolic blood pressure, diastolic blood pressure, eGFR, HbA1c, and weight. The multivariate Cox model was stratified by treatment assignment and trial (RENAAL or IDNT). A backward selection model was used with the significance set at $p<0.05$ to remove a covariate from the model. A multivariate Cox model was also used to assess the relationship between the residual month 6 systolic blood pressure and albuminuria. The residual systolic blood pressure was divided into four categories of approximate equal sample sizes and easy understandable thresholds: ≤ 130; 130 – 145; 145 – 160; > 160 mmHg. The residual albuminuria was divided into four categories as well: ≤ 0.75; 0.75 – 1.5; 1.5 – 3.0; >

3.0 g/g. For exploration of the hazard risk profile of the residual systolic blood pressure and albuminuria, a Cox model was used with systolic blood pressure ≤ 130 mmHg or albuminuria ≤ 0.75 g/g as a reference group. For testing of combined effects of residual month 6 systolic blood pressure and albuminuria, an interaction term was added to the model. The multivariate analyses were conducted in the overall population and stratified for treatment and trial to remove potential confounding as a result of treatment assignment or trial characteristics. In an additional analysis, the multivariate analysis was also conducted in the ARB treatment arm separately to examine whether changes in albuminuria that resulted from ARB treatment have the same relationship with long-term cardiovascular outcomes. Continuous variables are reported as means and standard deviations. Categorical variables are reported as numbers and percentages. All analyses were conducted with SAS version 9.0 (SAS Institute, Cary, NC).

Table 1: Baseline characteristics of the 2900 subjects included in the present analysis. The overall population is shown and the RENAAL and IDNT trials separately.

	Overall	RENAAL	IDNT
N	2900	1428	1472
Age (yr)	59.5 (7.6)	60.2 (7.4)	58.9 (7.7)
Female n,(%)	1010 (34.8)	524 (36.7)	486 (33.0)
Caucasian n,(%)	1774 (61.2)	690 (48.3)	1084 (73.6)
Black n,(%)	398 (13.7)	215 (15.1)	183 (12.4)
Hispanic n,(%)	335 (11.6)	265 (18.6)	70 (4.8)
Asian n,(%)	313 (10.8)	241 (16.9)	72 (4.9)
Smoking history n, (%)	513 (17.7)	258 (18.1)	255 (17.3)
Heart failure disease history n,(%)	174 (6.0)	75 (5.3)	99 (6.7)
MI disease history n, (%)	318 (11.0)	152 (10.6)	166 (11.3)
Systolic BP (mmHg)	154.5 (19.3)	153.0 (20.1)	155.9 (18.4)
Diastolic BP (mmHg)	84.1 (10.7)	82.7 (11.0)	85.5 (10.7)
eGFR (ml/min/1.73m2)	43.6 (15.5)	39.8 (12.4)	47.3 (17.3)
Serum Creatinine (mg/dL)	1.8 (0.5)	1.9 (0.5)	1.7 (0.6)
Hemoglobin (mg/dL)	12.7 (1.9)	12.5 (1.8)	13.0 (1.9)
HbA1c (%)	8.3 (1.7)	8.5 (1.6)	8.1 (1.7)
Total Cholesterol (mg/dL)	227.3 (56.2)	227.6 (55.5)	227.0 (56.9)
BMI (kg/m2)	30.2 (6.0)	29.7 (6.3)	30.7 (5.7)
UACR (mg/g)	1344 [659 – 2653]	1220 [566 -2592]	1462 [748 – 2716]

Abbreviations: BP, blood pressure; UACR, urinary albumin to creatinine ratio.
Values are expressed as mean with standard deviation. UACR is expressed as median with inter-quartile range

Results

Baseline characteristics and blood pressure and albuminuria response

A total of 2900 patients had baseline and month 6 systolic blood pressure and albuminuria values available for analysis (1428 RENAAL; 1472 IDNT). The baseline characteristics of these participants are shown in table 1. Patients participating in these trials had similar baseline characteristics. A discordant response in blood pressure and albuminuria was found in a considerable proportion of patients. Of the ARB assigned participants, 211 subjects (17.3%) showed a reduction in systolic blood pressure but no reduction in albuminuria and 210 (17.2%) had no reduction in systolic blood pressure but a reduction in albuminuria. (table 2). In the conventional treatment group, 507 (30.1%) and 236 (14.0%) had a discordant response in blood pressure and albuminuria.

Table 2: Patient distribution (number of patients as well as % of total in parenthesis) according to change in albuminuria and systolic blood pressure during the first 6 months of therapy for the ARB and conventional treatment group. The sum of the numbers and percentage in the boxes indicate the proportion of all subjects with a concordant respectively discordant blood pressure and albuminuria response.

ARB treatment N=1218		**Change in systolic blood pressure**				
		< -15 mmHg	**-15 – 0 mmHg**	**0 – 15 mmHg**	**> 15 mmHg**	
Albuminuria change	**> -30%**	272 (22.3)	181 (14.9)	77 (6.3)	44 (3.6)	**70.1**
	-30 to 0%	85 (7.0)	**52.9** 106 (8.7)	53 (4.4)	**17.2** 36 (3.0)	
	0 to 30%	52 (4.3)	54 (4.4)	37 (3.0)	20 (1.6)	**29.9**
	> 30%	45 (3.7)	**17.3** 60 (4.9)	49 (4.0)	**12.6** 47 (3.9)	
		70.2		**29.8**		**100**

Conventional Treatment N=1682		**Change in systolic blood pressure**				
		< -15 mmHg	**-15 – 0 mmHg**	**0 – 15 mmHg**	**> 15 mmHg**	
Albuminuria change	**> -30%**	202 (12.0)	**34.5** 126 (7.5)	57 (3.4)	**14.0** 39 (2.3)	**48.5**
	-30 to 0%	133 (7.9)	119 (7.1)	99 (5.9)	41 (2.4)	
	0 to 30%	79 (4.7)	**30.1** 105 (6.2)	80 (4.8)	**21.3** 43 (2.6)	**51.5**
	> 30%	156 (9.9)	167 (9.3)	139 (8.3)	97 (5.8)	
		64.6		**35.4**		**100**

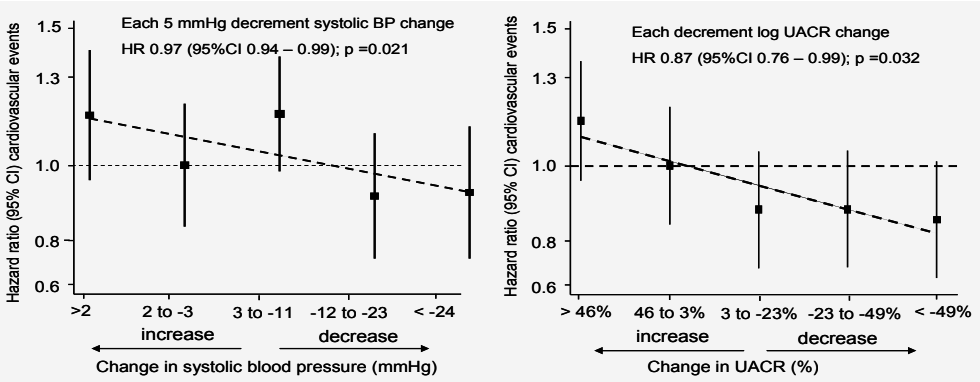


Figure 1: Relationship between month 6 change in blood pressure and albuminuria and cardiovascular outcome.

Boxes represent the point-estimate and the bars their 95% confidence interval. The variance of each quintile of change in albuminuria was calculated by using the absolute floating risk method. The regression line for the risk estimates according to quartiles in change in albuminuria was fitted using inverse variance weighting. The hazard ratio (95% confidence interval) reported in the figure is based on continuous data. The cardiovascular outcome was the composite of myocardial infarction, stroke, hospitalization for heart failure, or cardiovascular death.

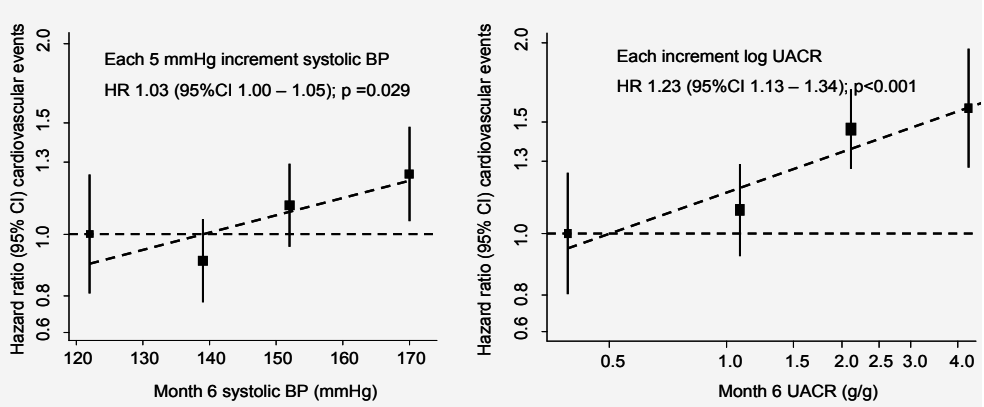


Figure 2: Relationship between residual month 6 blood pressure or albuminuria and cardiovascular outcome. Boxes represent the point-estimate and the bars their 95% confidence interval. The variance of each quartile of residual blood pressure or albuminuria was calculated by using the absolute floating risk method. The regression line for the risk estimates according to quartiles in change in albuminuria was fitted using inverse variance weighting. The cardiovascular outcome was the composite of myocardial infarction, stroke, hospitalization for heart failure, or cardiovascular death.

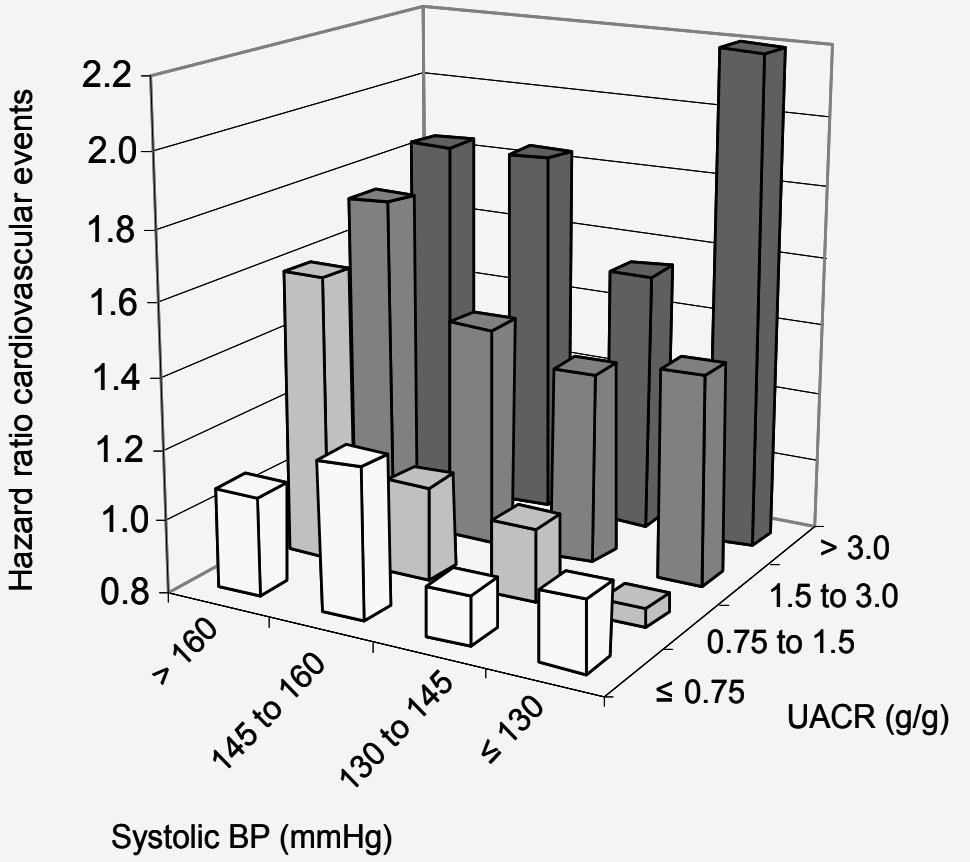
Systolic blood pressure and albuminuria reduction and cardiovascular outcome

A larger reduction in blood pressure during the first 6 months was independently associated with a lower risk for cardiovascular events (composite of myocardial infarction, stroke, hospitalization for heart failure, or cardiovascular death) in the long-term (figure 1). Each 5 mmHg reduction in blood pressure during the first 6 months was independently associated with a risk reduction of 3% (95%CI 1 - 6%; p=0.021) in cardiovascular events (figure 1). Additionally, a larger reduction in albuminuria during the first 6 months was independently associated with a lower risk for cardiovascular events in the long-term (figure 1). Each log unit decrement in albuminuria was associated with a 13% (95%CI 1 - 24%; p=0.032) risk reduction for cardiovascular events. Similarly, in patients treated with an ARB, each decrement in log albuminuria was associated with 20% (95%CI 4 - 34%; p=0.019) risk reduction for cardiovascular events. To establish the robustness of this finding we conducted a sensitivity analysis. Although all cardiovascular events were included in our analysis, we repeated the analysis limiting the cardiovascular events to only those arising after the 6 months time-point and noted a similar pattern.

Residual systolic blood pressure and albuminuria and cardiovascular outcome

The relationship between residual month 6 systolic blood pressure and albuminuria is shown in figure 2. A progressively lower cardiovascular risk was observed as the residual albuminuria decreased from 4.0 g/g to 0.5 g/g and the residual systolic blood pressure decreased from 170 mmHg to 120 mmHg. It should be noted however that the point estimate for cardiovascular risk in patients with an average month 6 systolic blood pressure of 120 mmHg was slightly higher compared to those with a systolic blood pressure of 140 mmHg.

The cardiovascular risk according to combined residual systolic blood pressure and albuminuria demonstrated that across all systolic blood pressure categories, a progressively lower cardiovascular risk was observed with a lower albuminuria level (figure 3). The presence of a low systolic blood pressure level in those who did not achieve a low albuminuria level did not confer additive protection against cardiovascular events. This was particularly evident in the strata of patients who achieved the systolic blood pressure goal below 130 mmHg. There was no interaction of the achieved month 6 albuminuria over systolic blood pressure (p=0.664).



	Month 6 systolic blood pressure (mmHg)			
Month 6 UACR (g/g)	**≤ 130**	**130 to 145**	**145 to 160**	**> 160**
≤ 0.75	234 (6.9)	472 (7.2)	234 (7.9)	145 (8.8)
0.75 to 1.5	126 (7.6)	223 (7.1)	186 (8.9)	117 (11.6)
1.5 to 3.0	117 (13.4)	243 (9.2)	231 (12.3)	232 (14.0)
> 3.0	44 (20.0)	120 (12.2)	111 (13.6)	165 (15.9)

Figure 3: Risk for cardiovascular events by achieved month 6 albuminuria and systolic blood pressure. The table below the graph shows the number of patients in each category with the corresponding cardiovascular event rate per 100 patient years between brackets.

Discussion

The data of this study indicate that a low residual systolic blood pressure in combination with a low residual albuminuria leads to optimal cardiovascular risk protection. However, using a blood pressure based titration regime, many patients do not achieve reductions in albuminuria despite a reduction in systolic blood pressure. This dissociation was observed in individuals treated with ARB treatment and conventional antihypertensive treatment. These data suggests that one should monitor not only the blood pressure but also the albuminuria response and adjust medication if necessary in order to optimally benefit in terms of cardiovascular outcome.

Supposedly, the albuminuria response depends at least to a certain extent on the blood pressure response. However, the results of this study indicate that in a significant proportion of patients an albuminuria response is discordant with the response in systolic blood pressure. The exact reasons for this discordance in response are difficult to establish from the current study, but several possibilities exist. First, it could be possible that the clinical blood pressure measurements do not accurately reflect true blood pressure and that the blood pressure response assessed by 24-hour ambulatory blood pressure, central blood pressure, or glomerular blood pressure monitoring is better coupled to the albuminuria response.[13-15] Second, it could be possible that differences in baseline parameters, diabetes control, or concomitant blood pressure lowering drugs differed across subgroups. The use of concomitant drugs and diabetes control was similar across the defined groups of blood pressure and albuminuria change which makes a possible interference with the discordant effect and the cardiovascular risk data unlikely. Interestingly, in a logistic multivariate analysis we found that body weight was the only baseline parameter associated with a discordant response. This might be expected as recent data show that higher body weight was associated with a greater albuminuria response while any change in blood pressure response upon RAAS inhibition has, to our knowledge, never been demonstrated.[16,17] Third, differences in tissue specific RAAS activity and differences in tissue penetration is another hypothetical option that may explain the disparity in blood pressure and albuminuria response within an individual. In this respect, the albuminuria response depends on the extent of intra-renal RAAS blockade while the systolic blood pressure response depends on systemic vasculature RAAS inhibition. Pre-clinical studies have indeed shown that inhibition of extra-renal RAAS plays an important role in mediating blood pressure control.[18] However, further studies establishing the relative roles of the intra-renal RAAS as opposed to the extra-renal RAAS are clearly warranted to dissect the underlying mechanism of disparity in albuminuria and blood pressure response within an individual. It is beyound dounbt that blood pressure should be tightly controlled to lower the risk of cardiovascular disease.[19] However, in addition to blood pressure, albuminuria is an independent cardiovascular risk predictor.[6] The results of our analysis confirm previous post-hoc analyses indicating that regimens that lower albuminuria independent of optimal blood pressure control are associated with a reduction in cardiovascular protection. The LIFE trial showed that reductions in albuminuria conferred by a losartan-based treatment explained one-fifth of the risk reduction on cardiovascular complications as compared to atenolol-based treatment.[7] In addition, a small study in patients with type 2

diabetes without hypertension and microalbuminuria demonstrated that sustained reductions in albuminuria distinguished individuals in their risk of cardiovascular events. The fact that blood pressure levels did not change or even rose during the course of this study, provides further support that reductions in albuminuria per sé were the driving parameter for cardiovascular protection.[20] Unfortunately however, there is no prospective randomized controlled data in patients with type 2 diabetes that determine whether albuminuria lowering in itself is associated with cardiovascular protection.

The clinical implication of our study is that a treatment approach concurrently aimed at optimal blood pressure and optimal albuminuria reduction within an individual will result in optimal cardiovascular protection. RAAS inhibitors are nowadays titrated towards the optimal blood pressure goal desired and tolerated.[21] The data of this study indicate that such an approach is not sufficient to achieve optimal cardiovascular protection as many patients who achieve optimal blood pressure goal do not have a sufficient albuminuria response and consequently remain at high cardiovascular risk. The results of this study suggest that a dual efficacy approach both pursuing optimal blood pressure as well as albuminuria reduction may further attenuate the risk of cardiovascular disease. Recent studies have shown that indeed increasing the dose of ARB's beyond the recommended dosing schedules may result in a levelling of the blood pressure response but a still increasing response in decreasing albuminuria.[22-24] Some caution is warranted. The ONTARGET trial results indicate that targeting blood pressure towards normalcy does not always guarantee that optimal cardiovascular protection is achieved.[25] However, one needs to realize that ACEi and ARBs may cause hypotension and/or increase serum potassium. Both effects may increase cardiovascular risk. Indeed, our data shows increased cardiovascular risk when systolic blood pressure levels fall below 120 mmHg. These data are in line with other post-hoc analyses of clinical trial data.[26-28] Whether the increased risk is the consequence of a too low systolic blood pressure or the consequence of other baseline co-morbidities warrants further research. Nevertheless, these effects may blunt the beneficial cardiovascular effects of albuminuria and blood pressure lowering. We therefore recommend that titration should be based on individual response rather than fixed titration schedules and that one not only focuses on the beneficial efficacy effects but also optimizes the response of drugs on parameters that negatively influence outcome.[29]

Some limitations of our analysis should be mentioned. This is a post-hoc analysis of trial data and the conclusions can only be considered as hypothesis generating. In addition, both the RENAAL and IDNT trials were not primarily designed to establish the effects of ARB or calcium antagonist therapy on cardiovascular endpoints (in particular the selection process focussed on renal patients). Strengths of the analysis include the large number of patients available and the rigorous methods of data collection, recording and analysis, allowing precise estimation of the effect sizes.

Conclusions

The systolic blood pressure and albuminuria response to ARB therapy does not always run in parallel. The cardiovascular risk is dependent on adequate blood pressure control but also showed a clear dependence on the achieved albuminuria regardless of the level of systolic blood pressure. These results suggest that therapies intervening in the RAAS with the aim to improve cardiovascular outcomes should not only titrate the drug to the lowest blood pressure goal wanted but may require a dual approach of lowering both blood pressure and albuminuria.

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References

1. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009 Aug;20:1813-21.

2. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. heart outcomes prevention evaluation study investigators. Lancet. 2000 Jan 22;355:253-9.

3. Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. Lancet. 2007 Sep 8;370:829-40.

4. Eijkelkamp WB, Zhang Z, Remuzzi G, et al. Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: Post hoc analysis from the reduction of endpoints in NIDDM with the angiotensin II antagonist losartan (RENAAL) trial. J Am Soc Nephrol. 2007 May;18:1540-6.

5. Laverman GD, Andersen S, Rossing P, Navis G, de Zeeuw D, Parving HH. Renoprotection with and without blood pressure reduction. Kidney Int Suppl. 2005 Apr;(94):S54-9.

6. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004 Aug 24;110:921-7.

7. Olsen MH, Wachtell K, Ibsen H, et al. Reductions in albuminuria and in electrocardiographic left ventricular hypertrophy independently improve prognosis in hypertension: The LIFE study. J Hypertens. 2006 Apr;24:775-81.

8. Brenner BM, Cooper ME, de Zeeuw D, et al. The losartan renal protection study--rationale, study design and baseline characteristics of RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan). J Renin Angiotensin Aldosterone Syst. 2000 12;1:328-35.

9. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 09/20;345:861-9.

10. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-

receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 09/20;345:851-60.

11. Rodby RA, Rohde RD, Clarke WR, et al. The irbesartan type II diabetic nephropathy trial: Study design and baseline patient characteristics. for the collaborative study group. Nephrol Dial Transplant. 2000 Apr;15:487-97.

12. Easton DF, Peto J, Babiker AG. Floating absolute risk: An alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Stat Med. 1991 Jul;10:1025-35.

13. Agarwal R. Ambulatory blood pressure and cardiovascular events in chronic kidney disease. Semin Nephrol. 2007 Sep;27:538-43.

14. Agarwal R. Home and ambulatory blood pressure monitoring in chronic kidney disease. Curr Opin Nephrol Hypertens. 2009 Nov;18:507-12.

15. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the conduit artery function evaluation (CAFE) study. Circulation. 2006 Mar 7;113:1213-25.

16. Holtkamp FA, Lambers Heerspink HJ, Laverman GD, et al. Body mass index is a predictor of angiotensin receptor blocker (ARB) induced albuminuria reduction. American Society of Nephrology, Denver. 2010 November.

17. Mallamaci F, Ruggenenti P, Perna A, et al. ACE inhibition is renoprotective among obese patients with proteinuria. J Am Soc Nephrol. 2011 Jun;22:1122-8.

18. Crowley SD, Gurley SB, Oliverio MI, et al. Distinct roles for the kidney and systemic tissues in blood pressure regulation by the renin-angiotensin system. J Clin Invest. 2005 Apr;115:1092-9.

19. Neal B, MacMahon S, Chapman N, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. blood pressure lowering treatment trialists' collaboration. Lancet. 2000 Dec 9;356:1955-64.

20. Zandbergen AA, Vogt L, de Zeeuw D, et al. Change in albuminuria is predictive of cardiovascular outcome in normotensive patients with type 2 diabetes and microalbuminuria. Diabetes Care. 2007 Dec;30:3119-21.

21. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003 Dec;42:1206-52.

22. Burgess E, Muirhead N, Rene de Cotret P, et al. Supramaximal dose of candesartan in proteinuric renal disease. J Am Soc Nephrol. 2009 Apr;20:893-900.

23. Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: A randomized controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol. 2007 Jun;18:1889-98.

24. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Int. 2005 Sep;68:1190-8.

25. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008 Apr 10;358:1547-59.

26. Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the irbesartan diabetic nephropathy trial. J Am Soc Nephrol. 2005 Jul;16:2170-9.

27. Lewis JB. Blood pressure control in chronic kidney disease: Is less really more? J Am Soc Nephrol. 2010 Jul;21:1086-92.

28. Sleight P, Redon J, Verdecchia P, et al. Prognostic value of blood pressure in patients with high vascular risk in the ongoing telmisartan alone and in combination with ramipril global endpoint trial study. J Hypertens. 2009 Jul;27:1360-9.

29. Lambers Heerspink HJ, de Zeeuw D. Dual RAS therapy not on target, but fully alive. Nephron Clin Pract. 2010;116:c137-42.

4

An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function

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Abstract

Intervention in the Renin-Angiotensin-Aldosterone-System (RAASi) is associated with slowing of progressive renal function loss. However, during therapy initiation, RAASi may induce an acute fall in glomerular filtration rate (GFR). We hypothesize that this initial fall in GFR upon RAASi reflects a renal hemodynamic effect that is associated with slower long-term renal function decline.

We conducted a post-hoc analysis of the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial, studying the relation between the initial fall in estimated GFR (eGFR) from baseline to month 3 and the long-term eGFR slope.

Patients assigned to losartan had a 0.73 ml/min/1.73m2 greater acute fall in eGFR during the first 3 months (p=0.031) compared to patients assigned to placebo, but a 0.8 ml/min/1.73m2/year slower long-term mean eGFR decline thereafter (-4.2 (95%CI -3.9 - 4.6) versus -5.0 (-4.7 - 5.4) ml/min/1.73m2/year; p<0.001). A large inter-individual difference in acute eGFR change was noticed. When subjects allocated to losartan were divided in tertiles of initial fall in eGFR, the long-term eGFR slope calculated from baseline was higher in subjects with an initial fall compared to those with an initial rise in eGFR: - 5.2(-5.8 - - 4.7) vs -4.1 (-4.7 - -3.6) vs. -3.6(-4.1 - -3.0; p<0.001), respectively. However, when eGFR decline was calculated from 3 months to the final visit, thus excluding the initial eGFR effect, subjects with a large initial fall in eGFR had a significant less steep slope compared to those with a moderate fall or rise in eGFR: (-3.6 (-4.2 - -3.1) vs, -3.9 (-4.4 – -3.3) vs. -4.4 (-5.0 – -3.9) ml/min/1.73m2/year), respectively.

In conclusion, an initial fall in eGFR during angiotensin receptor blocker treatment is associated with a subsequent slower rate of eGFR loss. Therefore, interpretation of trial results relying on slope based GFR outcomes should separate the initial drug induced GFR change from the subsequent long-term effect on GFR.

Keywords

Diabetic nephropathy, Glomerular filtration rate, Serum creatinine, Renal insufficiency, Chronic kidney disease, Angiotensin receptor blocker

Introduction

Diabetic nephropathy is the most common cause of end-stage kidney disease. Agents that block the Renin-Angiotensin-Aldosterone-System (RAAS) can prevent the onset and progression of nephropathy, attenuate deterioration of kidney function, and improve survival in patients with diabetes.[1-4]

Data from small scale studies have suggested that treatment with blood pressure lowering medication, including ACE-inhibitors or angiotensin-II receptor blockers (ARBs) is associated with an initial fall in glomerular filtration rate (GFR) or increase on serum creatinine levels, most likely resulting from a reduction in intraglomerular pressure.[5-7] In daily practice, a rise in serum creatinine may inappropriately raise safety concerns that prevent clinicians from using sufficiently high doses of ACE inhibitors or ARBs or from continuing treatment altogether. A systematic review showed that a rise in serum creatinine of up to 30% of baseline levels is no reason for concern, provided serum electrolytes (principally potassium) remain within normal limits.[8] A small-scale study in patients with chronic kidney disease even indicates that the magnitude of initial fall in GFR is inversely related to the long-term slope of GFR decline and is reversible after termination of RAAS blockade.[9] These data do not only show that the initial fall in GFR is hemodynamic rather than structural, but also suggest that the decline can, in fact, serve as an early marker of subsequent slower decline of long-term renal function obtained from RAAS inhibitor treatment. Evidence from large scale placebo controlled trials to support this hypothesis is, however, lacking.

The Reduction in Endpoints in Non Insulin Dependent Diabetes Mellitus with the Angiotensin-II Antagonist Losartan (RENAAL) trial investigated the effects of the ARB losartan versus placebo. The presence of a baseline period without RAAS inhibitor treatment and the availability of serum creatinine values on baseline and every 3 months during therapy, allows us to study the associations between treatment induced short-term responses in estimated GFR (eGFR) on the one hand and its long-term renal function decline on the other.

Methods

RENAAL study design

The RENAAL study was a double-blind, randomized, placebo-controlled trial that was designed to evaluate the renoprotective effects of a losartan-based antihypertensive regimen compared with a traditional blood pressure-lowering regimen in patients with type 2 diabetes, hypertension, and nephropathy. The study design, inclusion and exclusion criteria, and results have been reported elsewhere.[1,10] In brief, participants were considered to have type 2 diabetes if they were over 30 years old at the time of diagnosis of diabetes, had no history of ketoacidosis and did not use insulin therapy within 6 month after diagnosis. A serum creatinine between 1.3 and 3.0 mg/dL (1.5 to 3.0 mg/dL for males more than 60 kg), urinary albumin:creatinine ratio from a first morning specimen of at least 300 mg/g, HbA1c < 12% and age between 31 and 70 years were part of the inclusion criteria. After a 6-week screening phase, patients were randomly assigned to either losartan 50 mg (titrated to 100 mg after 4 weeks) or placebo. Additional antihypertensive medications (calcium channel blockers, β-blockers, centrally acting agents, and diuretics, excluding angiotensin-converting enzyme inhibitors or other angiotensin receptor blockers) were permitted during follow-up to reach the blood pressure goal of < 140/90 mmHg (systolic/diastolic). The mean follow-up duration was 3.4 year with a range of 2.3 to 4.6 year. The RENAAL trial was conducted according to the principles outlined in the Declaration of Helsinki. All patients signed informed consent. The protocol was approved by all relevant ethics committees.

Study visits, measurements and outcomes

Participants were seen at a screening visit, randomization visit, at 1 and 3 months after randomization and subsequently at 3 months intervals. At each visit serum creatinine and electrolytes were measured. The MDRD equation was used to estimate GFR.[11] The dose of losartan was titrated towards the maximum recommended dose of 100 mg at the first month visit. The acute change in eGFR was assessed from baseline to month 3, 2 months after institution of the maximum recommended dose of losartan.[10] Renal events were defined as a confirmed doubling in serum creatinine from baseline or ESRD, which was defined as chronic dialysis or renal transplantation. All endpoints were adjudicated by an independent outcome committee.

Statistical analyses

The difference in short-term and long-term eGFR change between placebo and losartan was calculated from baseline to month 3 and from month 3 to month 39. The difference in long-term eGFR slope between both treatment groups was estimated by a linear mixed effects model with random intercepts and random slopes. Since an acute fall in eGFR was only observed in individuals assigned to losartan, we investigated which factors predicted an initial fall in eGFR during losartan therapy. A multivariable model was used for this purpose. The following covariates were included in the model: age, gender, BMI, log transformed UACR, systolic and diastolic blood pressure, hemoglobin, total cholesterol, diuretic use at baseline,

and change from baseline to month 3 in log transformed UACR, systolic and diastolic blood pressure. Baseline characteristics that were statistically significantly associated with an acute fall in eGFR were selected for the multivariable regression model. Baseline characteristics not associated with eGFR decline in univariate analyses were step-wise added to the multivariable model to test their inclusion for statistical significance. Subsequently, we questioned whether those individuals with a more pronounced acute fall in eGFR showed a more stable course during long-term follow-up. Therefore, we compared the long-term eGFR slope for losartan treated individuals within subgroups (tertiles) of acute fall in eGFR. This approach was aimed at identifying subgroups with identical number of patients to increase the power of the analysis while minimizing the risk of bias. The long-term eGFR slope in each tertile of acute fall in eGFR was estimated by a linear mixed effects model with random intercepts and random slopes. To assess whether the long-term slope correlated with the acute eGFR fall independently of other patient characteristics or response parameters, the initial fall in eGFR was controlled for various covariates including baseline eGFR, diastolic blood pressure, hemoglobin, gender, log transformed UACR and month 3 change in log transformed UACR. In a sensitivity analysis eGFR was replaced for serum creatinine. Means and SD are provided for continuous variables, whereas number of patients and percentages are provided for class variables. A p-value ≤ 0.05 two sided was used to indicate statistical significance. All analyses were conducted with SAS version 9.1 software (SAS Institute, Cary, NC).

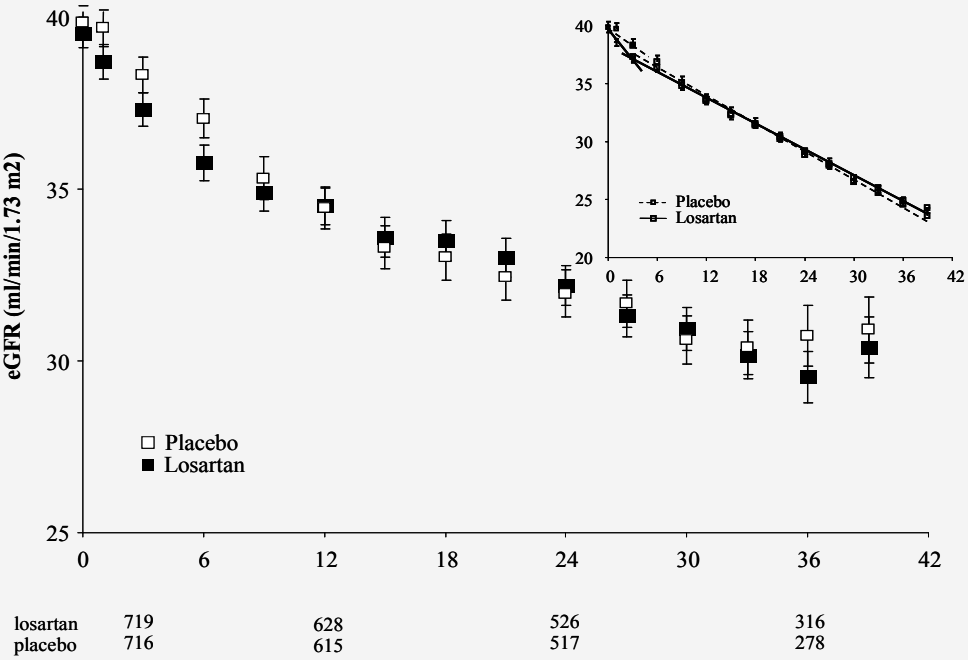

Figure 1: Mean eGFR levels through 39 months among patients who were assigned to receive losartan and placebo. The data and slope shown in the insert display the calculated eGFR data by linear mixed effects model. The long-term eGFR slopes in the losartan and placebo group are calculated from month 3 in the current analysis. The long-term eGFR decline originally reported by Brenner et.al [1] was calculated from baseline which explains the slight differences between the original publication and the current report.

Results

Course of estimated glomerular filtration rate in losartan and placebo treated individuals

The eGFR course during the RENAAL trial is shown in figure 1. The fall in eGFR three months after start of treatment was greater in losartan treated individuals compared to placebo (2.3 (95%CI 2.7 - 1.8) versus 1.6 (2.0 - 1.1) ml/min/1.73m2, respectively, p=0.031). The initial fall in eGFR was inversely associated with the long-term eGFR slope, such that the long-term eGFR slope in the losartan group was significantly smaller compared to placebo (-4.2 (95%CI -3.9 - -4.6) versus -5.0 (-4.7 - -5.4) ml/min/1.73m2/year; p<0.001, respectively).

Predictors of an acute fall in estimated glomerular filtration rate

The initial change in eGFR in the losartan group showed a wide variability: mean -2.3 (95%CI –14.6 – 12.5) ml/min/1.73 m2. In univariate analysis, urinary albumin:creatinine ratio (UACR) and month 3 change in UACR showed the strongest associations with the degree of the initial eGFR fall (table 1). In multivariable analysis, male gender, a higher baseline eGFR, UACR, and diastolic blood pressure, a lower hemoglobin and a larger month 3 decline in UACR were statistically significantly associated with a larger acute fall in eGFR.

Table 1: Independent predictors of initial eGFR change in losartan group calculated in univariable and multivariable regression model.

	Regression Coefficient	p-value
Univariable adjustment		
Urinary albumin:creatinine ratio	-1.157	<0.001
Systolic BP	-0.040	0.002
Hemoglobin	0.333	0.011
Total cholesterol	-0.009	0.029
Month 3 change UACR	1.640	<0.001
Month 3 change systolic blood pressure	0.057	<0.001
Month 3 change diastolic blood pressure	0.103	<0.001
Multivariable adjustment*		
Urinary albumin:creatinine ratio	-0.213	0.001
Hemoglobin	0.199	0.012
Month 3 change UACR	0.169	<0.001
Gender	0.086	0.036
eGFR	-0.155	<0.001
Diastolic blood pressure	-0.085	0.034

* Covariates are shown with a significant contribution to the multivariable model.

Abbreviations: UACR, urinary albumin:creatinine ratio

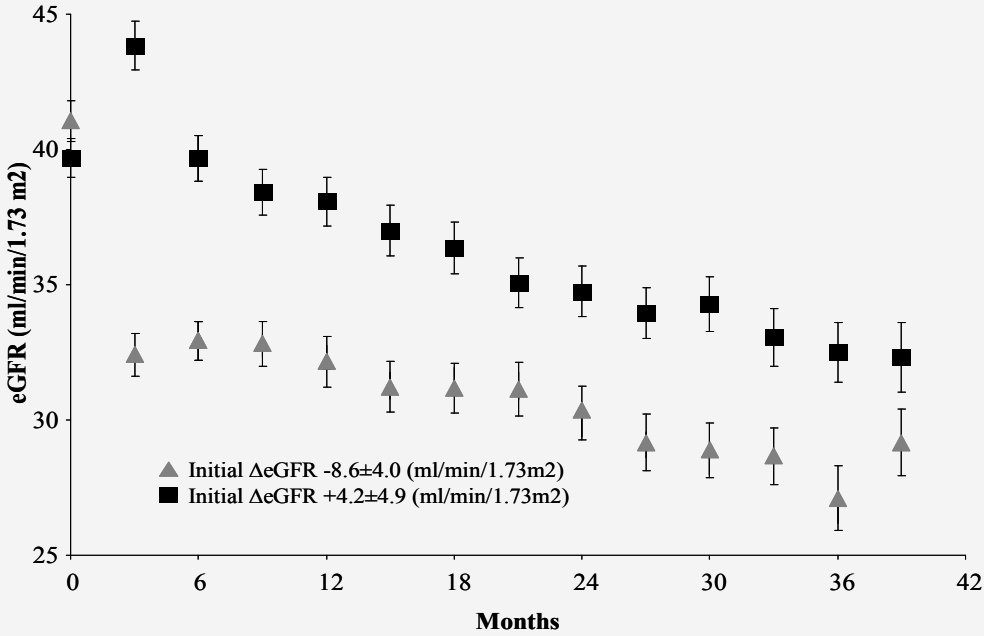

Figure 2: Mean eGFR levels through 39 months in patients assigned to losartan therapy with a decline (-8.6 ±4.0 ml/min/1.73m^2) or rise in eGFR (+4.2 ±4.9 ml/min/1.73m2) from baseline to month 3.

Effect of acute fall in estimated glomerular filtration rate on long-term renal function decline

To assess whether a more pronounced acute fall in eGFR during losartan therapy was associated with a more stable long-term eGFR course, patients assigned to losartan were stratified in tertiles according to the initial change in eGFR. The baseline characteristics of the losartan participants with available baseline and month 3 eGFR values are shown in table 2. Patients with a larger acute fall in eGFR had a significantly higher UACR, eGFR, and systolic BP at baseline and had greater reduction in UACR and systolic blood pressure after 3 months compared to those with a moderate fall or rise in eGFR.

In participants allocated to losartan, the mean eGFR at the median time (month 33) was lower in patients with an initial decline compared to those with an initial rise in eGFR: 28.7 (95%CI 26.3 – 31.0) versus 33.0 (95%CI 30.9 – 35.2; p=0.007) (figure 2). In addition, when the eGFR slope was calculated from baseline, eGFR decline was higher in subjects with an initial fall compared to those with an initial rise in eGFR -5.2(95%CI -5.8 to - 4.7) vs -3.6(95%CI -4.1 to -3.0; p<0.001).

Table 2: Baseline characteristics of losartan assigned patients by tertiles of initial fall in eGFR.

Variable	Tertiles of initial fall in eGFR		
Tertiles	**1**	**2**	**3**
Δ eGFR(ml/min/1.73m2)	-8.6 (4.0)	-2.4 (1.3)	+4.2 (4.9)
N	239	240	240
Age (years)	59.1 (7.5)	60.3 (7.5)	60.6 (7.0)
Gender (% male)	154 (64.4)	140 (58.3)	146 (60.8)
eGFR (ml/min/1.73m2)	41.1 (12)	38.0 (13)	39.7 (11)
Systolic BP (mmHg)	153.6 (20)	152.6 (19)	149.2 (17)
Diastolic BP (mmHg)	82.7 (11)	82.5(9.7	81.8(10.8)
Serum creatinine (mg/dl)	1.8 (0.5)	1.9 (0.5)	1.8 (0.5)
UACR (mg/g) [median; IQR]	1525 [587-3417]	1359 [627-2900]	893 [480-1692]
Hemoglobin (mg/dl)	12.4 (1.9)	12.4 (1.8)	12.7(1.8)
Total cholesterol (mg/dl)	232.3 (62)	226.4 (49)	221.8 (53)
HbA1c (%)	8.4 (1.6)	8.6 (1.6)	8.5 (1.7)
Diuretic (n, %)†	142 (59.4)	144 (60.0)	137 (57.1)
β-blocker (n, %)†	51 (21.3)	44 (18.3)	41 (17.1)
Calcium antagonist (n, %)†	172 (72.0)	178 (74.2)	164 (68.3)

Abbreviations: BP, blood pressure; UACR, urinary albumin:creatinine ratio.

Values are expressed as mean with standard deviation. UACR and change in UACR is expressed as median with inter-quartile range

†There were no marked differences in other blood pressure lowering therapies between losartan treated subjects during long-term follow-up

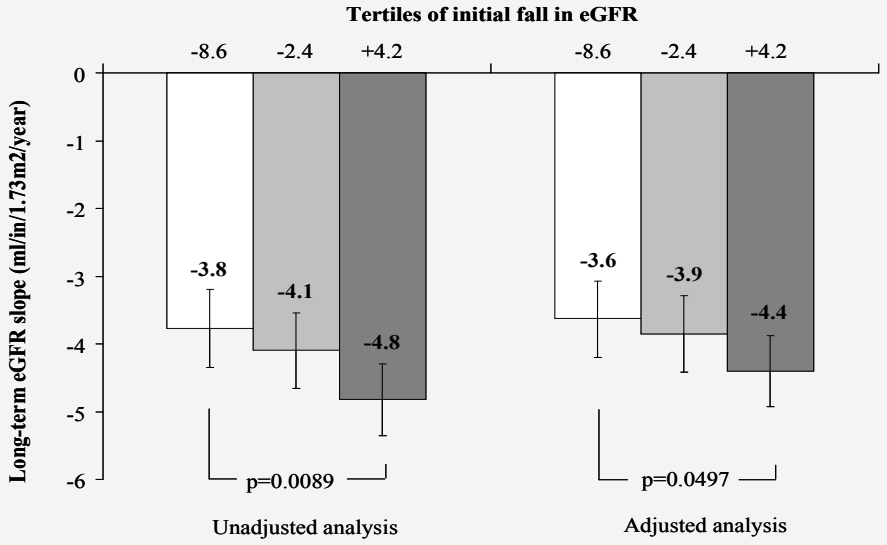

Figure 3: Long-term eGFR slope stratified by acute fall in eGFR in losartan assigned patients. Adjustment for covariates in the multivariable mixed effects model included gender, eGFR, diastolic blood pressure, hemoglobin, UACR and month 3 change in UACR. The numbers in each bar reflect the mean long-term eGFR slope.

A different pattern emerged when the initial eGFR effect was excluded and long-term eGFR decline was calculated from 3 months to the final visit. In unadjusted analyses, patients with a large initial fall in eGFR showed a more stable long-term eGFR course compared to patients with a moderate fall or an increase in initial eGFR (-3.8 (95%CI -4.4 to -3.2) vs -4.1 (95%CI -4.7 to -3.6) vs -4.8 (95%CI -5.4 to -4.3) ml/min/1.73m2, respectively, p=0.0094 for tertile 1 vs. 3). A multivariable analysis, adjusting for baseline characteristics and response parameters demonstrated that an initial steeper fall in eGFR remained statistically significantly associated with a more stable long-term eGFR course (figure 3). This correlation between the initial eGFR fall with long-term eGFR decline was exclusively observed in losartan treated patients. No correlation was observed between the acute fall in eGFR and long-term eGFR decline in placebo treated subjects nor was there any association between an acute fall in eGFR and long-term eGFR slope other than defined by a fall from baseline to month 3. The results of a sensitivity analysis using serum creatinine instead of eGFR were similar to the primary analysis. In stead of looking at eGFR changes over time we could also analyze the data on hard outcomes (doubling of serum creatinine or End Stage Renal Disease (ESRD)). When the overall population was divided in tertiles, the rate of renal events was higher in those with an initial fall compared to those with an initial rise in eGFR. However, in patients with an initial fall in eGFR the rate of renal events was profoundly attenuated in losartan treated patients compared to placebo. In contrast, in those with an initial rise in eGFR, renal event rate was almost similar between both treatment groups (table 3).

Table 3: Renal events (doubling of serum creatinine or ESRD) according to tertiles of initial change in eGFR in losartan and placebo allocated patients.

	Losartan		Placebo	
Mean (sd) initial eGFR change (ml/min/1.73m2)*	Events (%)	Event rate (per 100 patient*year)	Events (%)	Event rate (per 100 patient*years)
-8.3 (2.7)	98 (39.2)	15.6	113 (49.6)	21.6
-2.1 (1.3)	73 (29.7)	10.8	86 (36.9)	13.8
+4.6 (4.8)	46 (20.6)	6.9	54 (21.2)	7.3

* The mean initial eGFR change in each tertile differ from those presented in table 2 since the tertiles of initial eGFR change presented in table 3 were created in the overall population (losartan and placebo groups)

Discussion

In this study we demonstrated that initiation of antihypertensive therapy with an angiotensin receptor blocker induces an acute fall in estimated glomerular filtration rate that is inversely correlated with renal function decline during long-term follow-up. Specifically, the greater the acute eGFR fall, the slower the rate of long-term eGFR decline. This relationship is independent of other risk markers or changes in risk markers for progression of renal disease such as blood pressure and albuminuria.

The pharmacological effects of RAAS blockers on the GFR course can be best explained by a two-slope model of an acute fall in GFR up to 3 months and an attenuation of the long-term GFR slope until end of treatment. The acute fall in GFR could be of structural origin, due to a treatment induced reduction in number of functioning nephrons, or of hemodynamic origin. If the acute GFR fall induced by RAAS blockade is a hemodynamic response, treatment withdrawal should lead to an increase in GFR in the same order of magnitude as the initial fall. Indeed, a couple of studies demonstrated that after withdrawal of antihypertensive therapy, the GFR increased in the majority of patients and correlated with the initial GFR fall.[9,12] These data support the notion that the initial fall in GFR during RAAS blockade is of hemodynamic and not of structural origin.

The opposite hemodynamic and structural effects on GFR provide an ambiguous picture of the relationship between angiotensin receptor blockade and the rate of renal function decline. The acute reversible hemodynamic effect creates a pattern in which the long-term slope starting several months after randomization differs from the mean slope determined from baseline to study end. Indeed we observed that within losartan treated subjects, the long-term renal function slope determined from month 3 differed from the slope assessed from baseline to month 39. It should be remembered that the aim of renoprotective therapies is to delay or prevent changes in renal structural function. Therefore, renoprotective therapies focus on attenuating the long-term structural renal function decline excluding the early hemodynamic effect. In this respect, losartan treated subjects with a larger fall in eGFR during the first 3 months had indeed a subsequent slower rate of long-term renal function decline. However, when the eGFR slope was calculated form baseline, eGFR decline was significantly higher in patients with an initial fall compared with those with an initial rise in eGFR. This may be attributed to the large initial hemodynamic effect which may have negated the long-term beneficial effect and obscured the effect on structural renal function. It is tempting to speculate that after a longer follow-up this becomes apparent in a crossing of the long-term slopes as we also observed for the losartan-placebo comparison. However, the relatively short follow-up period precludes the verification of this possibility. Because of the opposite reversible hemodynamic effects many drugs and dietary interventions exert, we recommend that clinical trials using GFR based slopes as outcome should report the slope of (long-term) renal function decline starting several months after randomization and verify the reversibility of the initial (hemodynamic) effect by determining eGFR several months after treatment discontinuation.

Similar opposite short-term and long-term effects of different interventions on GFR decline

have been observed in past clinical trials. In the Modification of Diet in Renal Disease (MDRD) study, non-diabetic patients assigned to a low protein diet had a faster mean decline in GFR during the first four months but a slower mean GFR decline thereafter. Because the opposite directions of a low protein diet on GFR balanced each other, the primary comparison of the MDRD study was judged to be inconclusive.[11,13] Apperloo et al. showed in non-diabetic renal patients that patients treated with an ACE-inhibitor showed an acute initial fall in GFR. Again this fall was highly variable among the different patients. Those patients with a greater initial fall in GFR had a significant less steep GFR slope during long-term follow-up.[9] A systematic review of 12 randomized (small) clinical trials demonstrated that the acute fall in eGFR or rise in serum creatinine was inversely related with the subsequent rate of renal function decline. [8] The finding of our study substantiates the inverse correlation between the acute fall and chronic eGFR slope in losartan treated patients. The current study is thus the first large study in diabetes demonstrating the inverse association between initial GFR changes and long-term renal function decline.

The principle analyses were based on eGFR decline over time and not on the available hard renal endpoints like doubling of serum creatinine or ESRD. Selecting patients based on the initial change in serum creatinine (eGFR) directly influences the doubling of serum creatinine endpoint. It is therefore of no surprise that if we select those with an initial rise in serum creatinine (fall in eGFR) the renal event rate (doubling of serum creatinine or ESRD) is higher compared with patients with an initial fall in serum creatinine (rise in eGFR). However, if we take this into account and look at the group that has an initial fall in eGFR, we do see that the renal protective effect of losartan compared to placebo is much higher than in the patients that had a rise in eGFR. This indicates that a fall in eGFR on losartan is less worse than on placebo also with respect to hard renal outcomes as well.

What could be the mechanism for this hemodynamic acute fall in GFR and its relationship with long-term GFR decline? First of all, it could be possible that these effects are caused by a regression to the mean phenomenon. However, the fact that no correlation was observed between the acute fall in eGFR and long-term eGFR decline in the placebo group and no correlation between acute eGFR fall defined for other time intervals in the losartan group makes this assumption less likely. A physiological explanation is that in the presence of diabetes and hypertension, a dysfunction of the autoregulation of the afferent renal arteriole leads to increased transmission of the systemic blood pressure into the glomerular capillary network.[14] This results in increased intra-glomerular pressure and flow and eventually contributes to glomerular sclerosis and proteinuria.[15,16] Evidence that increased glomerular pressure and flow initiate this injury comes from animal studies demonstrating that reversing these hemodynamic processes, by means of ACE-inhibitor treatment or low protein diet, confer protection against structural damages.[17,18] In other words, control of intra-glomerular pressure, even in the presence of continued systemic hypertension, contribute to long-term stability of kidney function. RAAS blockade causes efferent renal vasodilation which in turn causes a reduction in intra-glomerular pressure, a reduction in filtration fraction, and an acute fall in GFR. Thus,

the reduction in intra-glomerular pressure may be the link between RAAS blockade induced acute reductions in GFR and the ability of this therapeutic strategy to delay long-term renal function decline. Furthermore, the variability in response may be the reflection of the difference in intra-glomerular pressure and/or the difference in the drug effect.

Some limitations need to be addressed when interpreting our findings. This is a post-hoc analysis of a large randomized controlled trial. Analyses according to the change in eGFR are no longer randomized, thus although we adjusted for a range of clinical characteristics between groups, residual confounding cannot be excluded. The results can therefore only be interpreted as hypothesis generating. Second, no data on eGFR slope is available in individual patients prior to enrolment in the RENAAL trial. Therefore we are not able to verify that patients with an acute eGFR fall had a less steep slope prior to initiation of therapy. We were therefore not able to distinguish between patients who respond to therapy compared to those who have progressive renal function loss. It must therefore be emphasized that a fall in eGFR can be the result of treatment or progressive renal function loss. One should therefore always interpret the eGFR fall in the context of other clinical conditions. Finally, we used the MDRD formula to calculate eGFR. It is known that such estimations suffer from both bias and imprecision.[19] Due to this imprecision, our results likely convey an underestimation of the strength of the association between the acute fall in GFR and its correlation with long-term renal function decline.

This study has several clinical implications. First, our data suggest that a fall in eGFR after start of RAAS inhibitor may be an indicator of the responsiveness to therapy instead of a safety issue in particular in the context when albuminuria and blood pressure are reduced as well. This can be interpreted as an encouragement to continue treatment, as long as other causes contributing to the fall in eGFR such as renal artery stenosis or diminished arterial blood volume or safety issues such as hyperkalemia can be excluded.[8] Second, our data have important consequences for the design and interpretation of clinical trials investigating the effects of drugs on GFR course. Calculation of the eGFR slope during antihypertensive treatment is based on the assumption that the slope is constant during follow-up. Our results, demonstrating a two-slope model of an acute hemodynamic eGFR response and a long-term eGFR decline, show that this assumption does not hold true. This highlights our recommendation to analyze and report the initial and long-term eGFR decline separately when determining the effects of antihypertensive agents on renal function. However, reports on the effects of antihypertensive agents on renal function still analyze and report the GFR from baseline to end of study.[20,21] Interpretation of changes in renal function in such reports is then based on both the hemodynamic and structural effect of the agent and provides a misleading picture of the effect of the antihypertensive agent on structural renal function.

Conclusions

An initial fall in estimated glomerular filtration rate during angiotensin receptor blocker treatment is independently inversely associated with less renal function loss during continued treatment. These opposite effects warrant caution in interpreting the results of clinical trials using slope outcomes defined by GFR. We recommend separate reporting of the drug induced short-term and long-term effect on GFR.

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References

1. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 09/20;345:861-9.

2. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 09/20;345:851-60.

3. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001 Sep 20;345:870-8.

4. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med. 2004 11/04;351:1941-51.

5. Bjorck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. BMJ. 1992 02/08;304:339-43.

6. Hillege HL, van Gilst WH, van Veldhuisen DJ, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: The CATS randomized trial. Eur Heart J. 2003 03;24:412-20.

7. Tarnow L, Rossing P, Jensen C, Hansen BV, Parving HH. Long-term renoprotective effect of nisoldipine and lisinopril in type 1 diabetic patients with diabetic nephropathy. Diabetes Care. 2000 12;23:1725-30.

8. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Arch Intern Med. 2000 03/13;160:685-93.

9. Apperloo AJ, de ZD, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney Int. 1997 03;51:793-7.

10. Brenner BM, Cooper ME, de Zeeuw D, et al. The losartan renal protection study--rationale, study design and baseline characteristics of RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan). J Renin Angiotensin Aldosterone Syst. 2000 12;1:328-35.

11. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method

to estimate glomerular filtration rate from serum creatinine: A new prediction equation. modification of diet in renal disease study group. Ann Intern Med. 1999 03/16;130:461-70.

12. Hansen HP, Rossing P, Tarnow L, Nielsen FS, Jensen BR, Parving HH. Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. Kidney Int. 1995 06;47:1726-31.

13. Short-term effects of protein intake, blood pressure, and antihypertensive therapy on glomerular filtration rate in the modification of diet in renal disease study. J Am Soc Nephrol. 1996 Oct;7:2097-109.

14. Christensen PK, Hansen HP, Parving HH. Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients. Kidney Int. 1997 Nov;52:1369-74.

15. Anderson S, Brenner BM. The role of intraglomerular pressure in the initiation and progression of renal disease. J Hypertens Suppl. 1986 12;4:S236-8.

16. Anderson S, Brenner BM. Intraglomerular hypertension: Implications and drug treatment. Annu Rev Med. 1988;39:243-53.

17. El-Nahas AM, Paraskevakou H, Zoob S, Rees AJ, Evans DJ. Effect of dietary protein restriction on the development of renal failure after subtotal nephrectomy in rats. Clin Sci (Lond). 1983 Oct;65:399-406.

18. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. Am J Med. 1982 03;72:375-80.

19. Freedberg DE. To eGFR or not to eGFR: Here is an intern‘s answer. Kidney Int. 2009 Jul;76:129-30.

20. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of a randomised controlled trial. Lancet. 2010 Apr 3;375:1173-81.

21. Heerspink HL, de Zeeuw D. Composite renal endpoints: Was ACCOMPLISH accomplished? Lancet. 2010 Apr 3;375:1140-2.

5

Both hypokalemia and hyperkalemia are associated with increased risk for cardiovascular outcomes during blood pressure lowering therapy: A post-hoc analysis of the RENAAL and IDNT trials

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Abstract

Treatment with angiotensin receptor blockers (ARB) and calcium channel blockers (CCB) is associated with cardiovascular protection. However, ARBs may induce an increase in serum potassium, while CCBs are reported to induce a decrease in serum potassium. Both hyperkalemia and hypokalemia are associated with increase in cardiovascular risk. We examined the association between on-treatment (ARB or CCB) serum potassium and subsequent cardiovascular (CV) risk.

A post-hoc analysis in the combined Reduction of Endpoints in non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials was performed. Patients with diabetes and nephropathy were randomized to ARB treatment (losartan in RENAAL and irbesartan in IDNT), CCB treatment (amlodipine in IDNT), or placebo. The impact of hypokalemia or hyperkalemia at month 3 on CV outcomes was assessed by multivariate Cox analysis.

At month 3, hyperkalemia had developed in 131 (11.4%) patients on ARB treatment and 47 (4.1%) on placebo ($p<0.001$ ARB vs. placebo). Hypokalemia developed in 13 (2.7%) patients on CCB treatment and 12 (1.0%) on placebo ($p=0.020$ CCB vs. placebo). Serum potassium levels between 5.0 and 5.5 and $\geq$ 5.5 mmol/L were associated with an increase in CV risk of 20% (HR 1.20; 95% CI 1.00-1.50; $p=0.054$) and 31% (HR 1.31; 95% CI 1.00-1.72; $p=0.049$). A potassium of <3.5 mmol/L at month 3 was associated with a 61% increase in CV risk (HR 1.61; 95% CI 1.01-2.59; $p=0.047$).

In conclusion, ARB or CCB treatment is associated with an increased likelihood of developing hyperkalemia or hypokalemia, respectively in patients with type 2 diabetes and nephropathy. In turn, both hypokalemia and hyperkalemia are associated with increased cardiovascular risk. Proper management of hypokalemia and hyperkalemia may be warranted since it may (further) reduce the cardiovascular risk.

Keywords

Serum potassium, Hyperkalemia, Hypokalemia, Angiotensin receptor blocker, Calcium channel blocker, Type 2 diabetes, Nephropathy, Cardiovascular disease

Introduction

Achieving optimal blood pressure control is a major therapeutic target in patients with diabetes and nephropathy. Inhibition of the Renin-Angiotensin-Aldosterone-System with either angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) is first choice therapy because of their distinct effects on both blood pressure and albuminuria. These effects are associated with long-term renal and cardiovascular protection.[1,2] Despite these beneficial effects, treatment with ACEi and/or ARBs raises serum potassium sometimes leading to hyperkalemia.[3,4] Hyperkalemia in turn may be associated with an increased risk of cardiovascular (CV) disease.[5] Patients with diabetes and nephropathy are particularly prone to develop hyperkalemia during RAAS inhibition, as illustrated by several studies.[6-9] Yet, no data are available whether hyperkalemia during RAAS inhibition is associated with an increased risk of cardiovascular events in this population.

Many patients with diabetes and nephropathy need more than one antihypertensive drug to achieve blood pressure targets. Calcium channel blockers (CCB) are frequently used to further lower blood pressure. However, despite the effective blood pressure lowering properties of these drugs, studies have suggested that CCBs lower serum potassium leading to hypokalemia.[10-13] Hypokalemia has been associated with an increased risk of cardiovascular events.[14] Whether hypokalemia during CCB therapy is associated with an increased risk of cardiovascular events is not established.

The aim of this study was to investigate the association between on-treatment (ARB and/or CCB) serum potassium and cardiovascular outcome during blood pressure lowering therapy in patients with type 2 diabetes and nephropathy participating in the Reduction of Endpoints in non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials.

Methods

Study design RENAAL and IDNT trials

This retrospective analysis consists of 3228 subjects with type 2 diabetes and nephropathy randomized in the multinational, double-blind RENAAL and IDNT trials. The detailed design, rationale, and study outcome for these trials have been previously published.[15-18] Both trials investigated the efficacy of an ARB primarily on renal outcomes and secondarily on cardiovascular outcomes in subjects with type 2 diabetes and nephropathy. In addition, the IDNT trial included a calcium antagonist (CCB, amlodipine) treatment arm. Inclusion criteria were essentially similar despite some minor differences. Patients eligible had type 2 diabetes and nephropathy, aged between 30-70 years, and had serum creatinine levels ranging between 1.3 and 3.0 mg/dL in the RENAAL trial (with a lower limit of 1.5 mg/dL for males) and 1.0 and 3.0 mg/dL in the IDNT trial (with a lower limit of 1.2 mg/dL for males). The proteinuria inclusion criterion for IDNT was a 24 hour urinary protein excretion of >900 mg, whereas RENAAL patients required a urinary albumin to creatinine ratio (UACR) derived from a first morning urine specimen of >300 mg/g or a 24 hour urinary protein excretion >500mg/day. Exclusion criteria for both trials were type 1 diabetes or non-diabetic renal disease. Patients in the RENAAL trial were randomly assigned to losartan 50 mg/day or placebo, while the IDNT trial randomly assigned patients to one of three treatment arms: irbesartan 75 mg/day, amlodipine 2.5 mg/day or placebo. After 4 weeks, blinded study medication was titrated towards losartan 100 mg/day or matched placebo in the RENAAL trial, and irbesartan 300 mg/day, amlodipine 10 mg/day or matched placebo in the IDNT trial. Other antihypertensive medications (with the exception of ACEi, ARB, or aldosterone antagonists) were allowed after the titration period to meet the blood pressure target of 140/90 mmHg in the RENAAL trial and 135/85 mmHg in the IDNT trial.

Cardiovascular outcomes

Cardiovascular outcomes were recorded in both trials and were defined as the composite of myocardial infarction, stroke, hospitalization for heart failure, cardiovascular death, or revascularization procedures. All cardiovascular outcomes were adjudicated by an independent blinded endpoint committee using rigorous outcome definitions.

Serum potassium during follow-up

Serum potassium was measured every 3 months in both trials. Hypokalemia was defined as a potassium level <3.5 mmol/L, modest hyperkalemia defined as a potassium level between 5.0 and 5.5, and hyperkalemia defined as a potassium level ≥5.5 mmol/L. We determined the relationship between the serum potassium level at month 3 and cardiovascular outcomes. The month 3 value was chosen since the effects of therapy were considered to be fully present at month 3 and relatively few cardiovascular events occurred before month 3. The cut-offs for hypokalemia and hyperkalemia are based on normal values derived from distributions in the population. However, patients with deranges in potassium even within the normal range may

already be at increased risk. In line with a previous study,[19] we also assessed the relationship between a serum potassium ≥ 5.0 mmol/L and CV outcome. Spurious hyperkalemia is a well described phenomenon in clinical practice. Since it is unlikely that subjects with a single erroneous measurement are at increased risk of cardiovascular disease we also calculated the association between repetitive serum potassium measurements ≥5.0 mmol/L or <3.5 mmol/L during follow-up and cardiovascular outcome.

Statistical Analysis

Baseline characteristics were compared across month 3 potassium concentrations by using one-way ANOVA or contingency table analysis, as appropriate. To identify parameters associated with the development of hyperkalemia or hypokalemia at month 3, a multivariate logistic regression model was performed excluding patients with hyperkalemia or hypokalemia at baseline. The backward selection method was used for selection of covariates in the final model (α=0.1). The multivariate logistic model included age, gender, duration of diabetes, serum potassium, systolic blood pressure, estimated Glomerular Filtration Rate (eGFR) (calculated with the Modification of Diet in Renal Disease formula), albumin, HbA1c, hemoglobin, UACR, treatment assignment, prescription of α-blockers, β-blockers, thiazide diuretics, potassium-sparing diuretics, loop diuretics, ACEi or ARBs, as well as month 3 changes in eGFR, UACR, and systolic blood pressure. A multivariate Cox model was used to assess the association between month 3 hypokalemia or hyperkalemia and cardiovascular outcomes using subjects who were normokalemic as a reference while adjusting for age, gender, race, diabetes duration, baseline serum potassium, treatment assignment, month 3 eGFR, month 3 UACR, month 3 systolic blood pressure, and thiazide-, loop-, and potassium sparing diuretics. A p-value ≤ 0.05 was used to indicate statistical significance. Analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

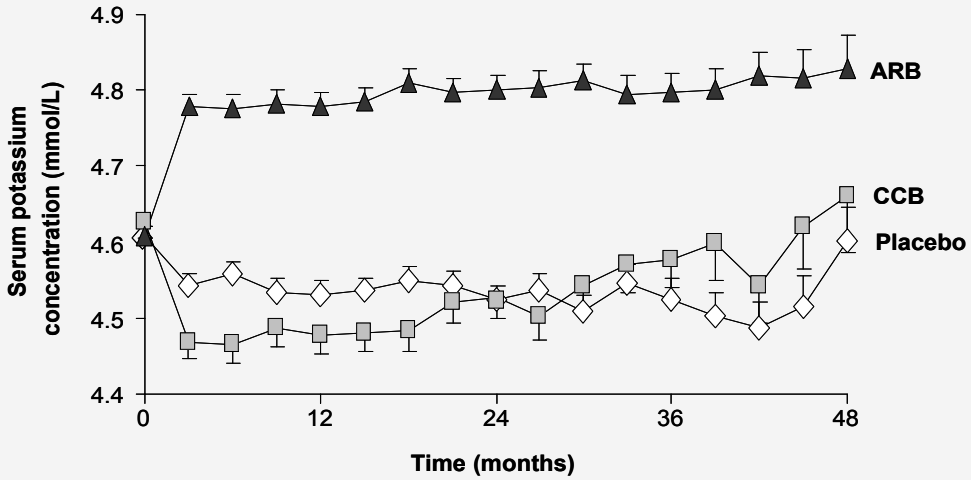

Figure 1: Mean serum potassium level during follow-up among patients who were assigned to angiotensin receptor blocker, calcium channel blocker or placebo therapy.
Bars represent standard errors.

Results

Serum potassium over time and characteristics of the study population

Serum potassium increased from 4.61 mmol/L to 4.78 mmol/L during the first 3 months in ARB treated patients ($p<0.001$ versus placebo) and remained stable from month 3 to the end of treatment. In contrast, CCB assigned patients showed a significant decrease in serum potassium level from 4.63 mmol/L to 4.47 mmol/L during the first 3 months ($p=0.009$ versus placebo), while this difference attenuated over time (figure 1). The proportion of patients with hyperkalemia at baseline was not statistically significant different among treatment groups. The proportion of subjects with hypokalemia at baseline in the CCB group was significantly lower compared to placebo (figure 2). The proportion of patients who developed hyperkalemia after 3 months ARB treatment (11.4%) was significantly higher than in the placebo group (4.1%; $p<0.001$), while the proportion of patients who developed hypokalemia was significantly higher in the CCB group (2.7%) compared to placebo (1.0%; $p=0.020$; figure 2).

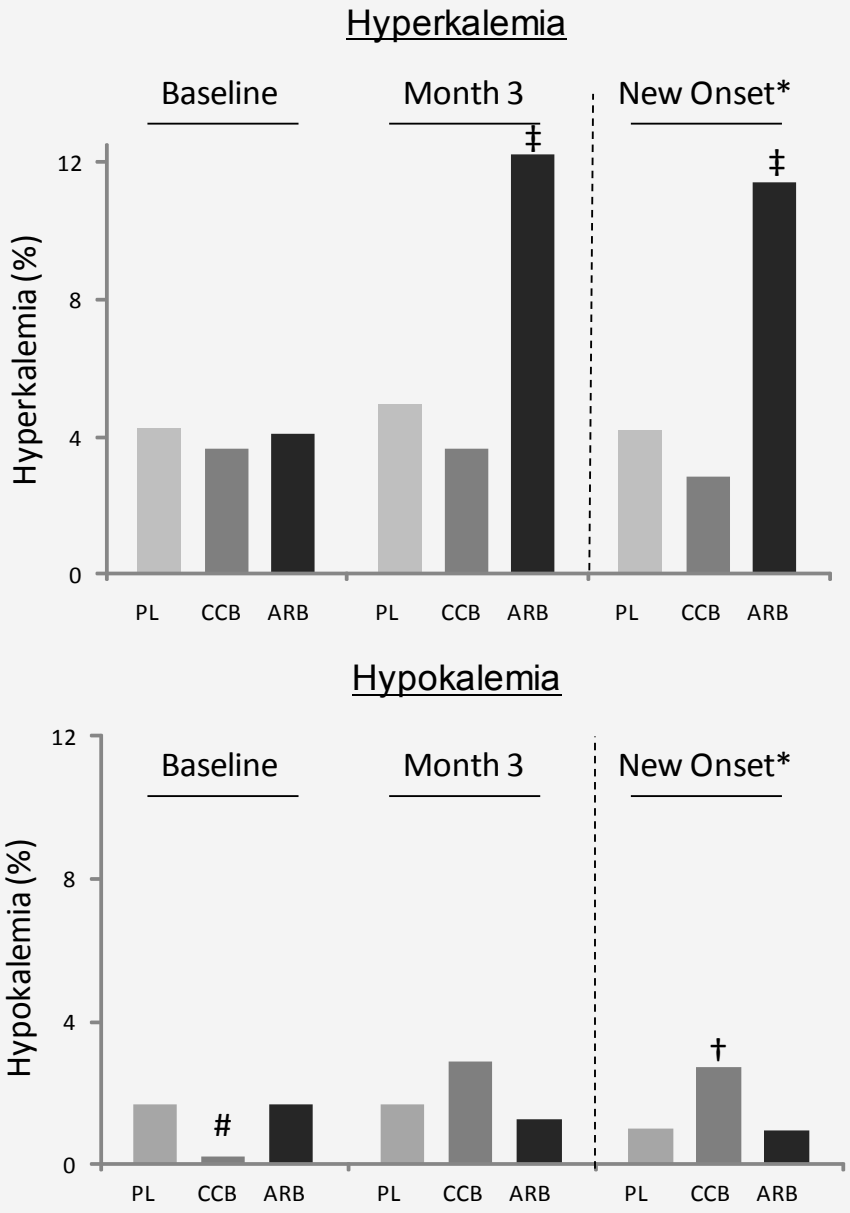

Figure 2: Proportion of patients in each treatment group with hyperkalemia and hypokalemia at baseline and month 3 in patients treated with placebo (PL), a calcium channel blocker (CCB) and an angiotensin receptor blocker (ARB). *New onset denotes the proportion of subjects who were normokalemic at baseline and developed respectively hyperkalemia or hypokalemia at month 3. Symbols indicate: ‡p<0.001; # p=0.011; †p=0.020

Table 1 shows the characteristics of the study population. Of the 2987 patients with available month 3 potassium values, 50 (1.7%) had hypokalemia, 2131 (71.3%) patients had serum potassium values in the normal range, 575 (19.3%) had modest hyperkalemia, and 231 (7.7%) patients had hyperkalemia. Across categories of increasing serum potassium levels at month 3, patients had higher baseline serum potassium and UACR, and lower diastolic blood pressure, eGFR, hemoglobin, and body mass index. In addition, they were less likely to be treated with thiazide diuretics, α-blockers, and ACE-inhibitors.

Table 1: Baseline and month 3 characteristics according to categories of month 3 serum potassium levels.

Baseline Characteristics	Serum potassium at month 3				
	<3.5 mmol/L (n=50)	3.5 to 5.0 5 mmol/L (n=2131)	5.0 to 5.5 mmol/L (n=575)	≥5.5 mmol/L (n=231)	P value
Age, yrs	59.3 (9.4)	59.3 (7.7)	59.9 (7.3)	59.0 (7.6)	0.319
Male, n (%)	33 (66.0)	1390 (65.3)	373 (64.9)	139 (60.2)	0.196
Race, n (%)					0.717
White	21 (42.0)	1314 (61.7)	351 (61.0)	143 (61.9)	
Black	19 (38.0)	327 (15.4)	60 (10.4)	16 (6.9)	
Hispanic	5 (10.0)	203 (9.5)	87 (15.1)	39 (16.9)	
Asian	4 (8.0)	219 (10.3)	63 (11.0)	28 (12.1)	
Other	1 (2.0)	67 (3.1)	14 (2.4)	5 (2.2)	
Systolic BP, mmHg	159.1 (23.3)	155.8 (19.7)	155.9 (20.5)	155.7 (19.4)	0.708
Diastolic BP, mmHg	89.5 (13.0)	85.1 (11.1)	83.4 (10.7)	83.4 (10.0)	<0.001
UACR, mg/g, median (IQR)	1320 [551-2261]	1297 [653-2504]	1447 [738-2929]	1651 [735-3256]	0.001
Serum potassium, mmol/L	3.81 (0.5)	4.51 (0.5)	4.90 (0.4)	4.99 (0.5)	<0.001
Serum creatinine, mg/dl	1.8 (0.6)	1.7 (0.5)	1.9 (0.5)	1.9 (0.5)	<0.001
eGFR, ml/ min/1.73m2	44.8 (16.1)	45.1 (16.2)	40.5 (14.1)	38.8 (13.8)	<0.001
HbA1C, %	8.4 (2.0)	8.3 (1.7)	8.4 (1.7)	8.1 (1.5)	0.077
Hemoglobin, mg/dL	13.0 (2.1)	12.9 (1.8)	12.5 (1.9)	11.9 (1.9)	<0.001
BMI	32.5 (7.0)	30.7 (6.0)	29.5 (5.9)	28.9 (5.9)	<0.001

Table 1 (continued)

Treatment at baseline					
Thiazide diuretics, n (%)	18 (36.0)	325 (15.3)	49 (8.5)	25 (10.8)	<0.001
K sparing diuretics, n (%)	0	47 (2.2)	11 (1.9)	3 (1.3)	0.523
Loop diuretics, n (%)	29 (58.0)	813 (38.2)	238 (41.4)	104 (45.0)	0.134
a-blockers, n (%)	12 (24.0)	354 (16.6)	88 (15.3)	21 (9.1)	0.002
Calcium channel blockers, n (%)	32 (64.0)	1155 (54.2)	310 (53.9)	127 (55.0)	0.783
β-blockers, n (%)	12 (24.0)	388 (18.2)	103 (17.9)	41 (17.7)	0.614
ARB, n (%)	2 (4.0)	70 (3.3)	16 (2.8)	3 (1.3)	0.094
ACEi, n (%)	30 (60.0)	1027 (48.2)	241 (41.9)	87 (37.7)	<0.001
Month 3 characteristics					
Systolic BP, mmHg	147.7 (23.7)	147.0 (19.2)	148.4 (20.4)	147.1 (20.3)	0.476
Diastolic BP, mmHg	82.6 (14.0)	80.8 (11.0)	80.1 (10.1)	78.8 (10.3)	0.021
UACR, mg/g, median (IQR)	1153 [492-2241]	1253 [555-2443]	1360 [587-2665]	1317 [580-2844]	0.331
eGFR ml/min/1.73m2	42.3 (18.8)	43.2 (17.2)	37.9 (14.7)	35.1 (14.1)	<0.001

Abbreviations are: ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, BP – blood pressure, UACR – albumin-creatinine ratio:

[a]Data are presented as means (SD) or numbers (%) or median [interquartile range]

Parameters associated with development of hypokalemia and hyperkalemia at month 3

A lower serum potassium level at baseline, assignment to CCB treatment, and prescription of β-blockers at baseline were independently associated with an increased likelihood of developing hypokalemia at month 3 (table 2). With respect to hyperkalemia, higher baseline serum potassium, assignment to ARB treatment, lower hemoglobin, and a larger month 3 reduction in eGFR were independently associated with an increased likelihood of developing hyperkalemia, while prescription of α-blockers was associated with a decreased likelihood (table 2).

Table 2: Parameters associated with incident hypokalemia (<3.5 mmol/L) or hyperkalemia (≥5.5 mmol/L) (ordered by decreasing significance based on $\chi 2$).

Risk marker of hypokalemia	Odds ratio (95%CI)	χ2	P value
Serum potassium, mmol/L	0.03 (0.01 – 0.09)	43.0	<0.001
Beta-blocker	2.8 (1.3 – 6.2)	6.5	0.011
Thiazide diuretics	2.4 (1.1 – 5.2)	4.5	0.033
Assignment to CCB treatment	2.6 (1.0 – 6.7)	4.0	0.045
Risk marker of hyperkalemia			
Serum potassium, mmol/L	7.1 (4.4 – 11.3)	66.7	<0.001
Assignment to ARB treatment	3.3 (2.3 – 4.9)	37.4	<0.001
Hemoglobin, mg/dL	0.8 (0.7 – 0.9)	24.6	<0.001
a-blocker use	0.5 (0.3 - 0.9)	5.5	0.019
Month 3 change eGFR (ml/min/1.73m2)	0.97 (0.95 – 0.99)	4.9	0.027

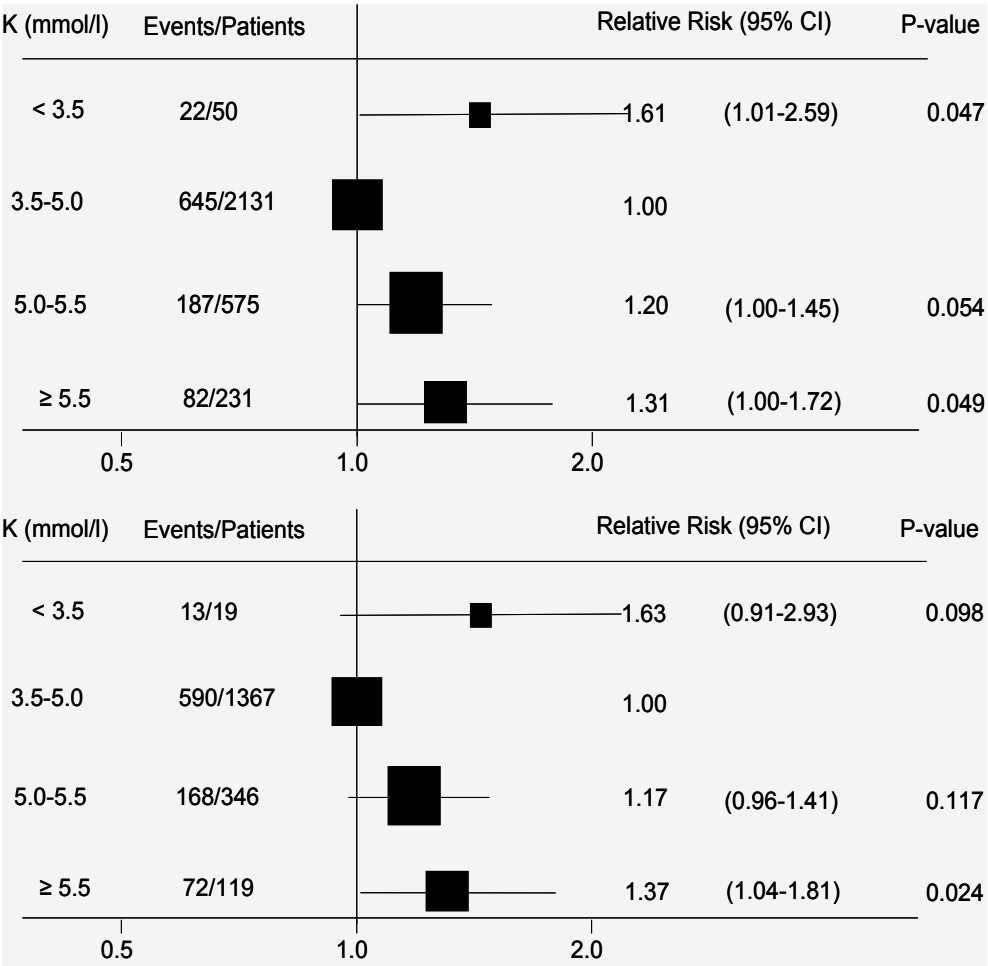

Figure 3: Month 3 serum potassium level and the risk for the composite cardiovascular endpoint (MI, HF, Stroke, CV death, Revascularization). Bars represent 95% Confidence Intervals. Figure 3A shows the relationship for all subjects included in the study. Figure 3B shows the relationship for the population who did not have hypokalemia or hyperkalemia at baseline.

Serum potassium during follow-up and the risk of cardiovascular outcomes

We subsequently analyzed whether hypokalemia or hyperkalemia at month 3 was associated with an increased risk of cardiovascular events. After adjustment for multiple risk parameters (most notably serum potassium, eGFR and UACR), CV risk was significantly increased in subjects who had hypokalemia (1.61; 95% CI 1.01-2.59; p=0.047), modest hyperkalemia (1.20; 1.00-1.50; p=0.054) and hyperkalemia (1.31; 1.00-1.72; p=0.049) as compared with those who had potassium levels in the normal range at month 3 (Figure 3A). Furthermore, when we selected those who developed hypokalemia, modest hyperkalemia or hyperkalemia, thus excluding subjects who already had hypokalemia or hyperkalemia at study entry, the risk for CV events associated with hypokalemia and hyperkalemia persisted (figure 3B).

We also analyzed CV risk according to month 3 serum potassium ≥ 5.0 mmol/L. A month 3 serum potassium ≥ 5.0 mmol/L was associated with a 23% ((HR 1.23; 1.03 – 1.45) p=0.019) increase in CV risk. We subsequently distinguished between subjects with a single elevated month 3 serum potassium and those with a serum potassium remaining elevated during follow-up in order to establish the existence of an exposure-risk relationship. It turned out that CV risk was particularly present in those subjects in whom serum potassium remained consistently above ≥ 5.0 mmol/L during follow-up (HR 1.30 (1.02 – 1.66); p=0.037) while the risk was not significantly elevated in those with a single elevated serum potassium measurement at month 3 (HR 1.13 (0.85 – 1.49) p=0.406) as compared with subjects who remained normokalemic. Likewise, subjects with a single hypokalemia measurement were at less risk compared with those with persistent hypokalemia during follow-up (HR 1.26 (0.70-2.28) and 1.91 (0.77-4.73), respectively).

Discussion

We demonstrated that in patients with diabetes and nephropathy ARB therapy increases serum potassium levels while treatment with a CCB causes a fall in serum potassium. Both the hypokalemia and hyperkalemia during CCB and ARB therapy are in turn associated with an increased risk of cardiovascular events. The risk for cardiovascular events associated with hyperkalemia started to increase at serum potassium levels above 5.0 mmol/L and further increased at levels above 5.5 mmol/L.

Angiontensin receptor blockers and hyperkalemia

The effects of ARB treatment on serum potassium are in line with other studies. Various studies have shown that intervention in the RAAS increases serum potassium, in particular in patients with diabetes or renal insufficiency.[6-9] The main effect of ARB treatment, i.e. blockade of the effect of angiotensin II, results in a decrease in aldosterone release. Thus, the increase in serum potassium is likely the result of less aldosterone induced potassium excretion in the distal nephron.[20] These effects are particularly dominant in patients with diabetes who are often volume expanded and have, as a result, already a suppressed circulatory RAAS activity.

The association between hyperkalemia and risk of cardiovascular events has been previously described in patients with heart failure as well. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial, candesartan increased the incidence of death or hospitalization due to hyperkalemia.[4] The increased risk of cardiovascular events associated with hyperkalemia must be interpreted in the context of the cardiovascular benefits afforded by ARB treatment, as well as the potential to lower the risk of hypokalemia which is by itself associated with cardiovascular events as well. We therefore advocate the continuous use of ARB treatment in patients with diabetes and nephropathy and recommend careful monitoring and appropriate treatment of hyperkalemia. Whether monitoring and prevention of hyperkalemia enhances the cardioprotective effects of ARBs requires further examination.

It is noteworthy that the risk for CV events already started to increase at levels above 5.0 mmol/L. This threshold indicates that even modest increases in serum potassium may already be significantly associated with an increased risk of cardiovascular events. These results are in clear contrast with a recent report down-playing the effect of ARB therapy on serum potassium levels and its relationship with cardiovascular outcomes.[21] We recommend that even small changes in serum potassium during ARB therapy should serve as a continuous reminder to be vigilant and are a signal to initiate appropriate measures to manage hyperkalemia. These include discontinuation or caution in prescribing therapies with hyperkalemic potential, such as potassium sparing diuretics, potassium supplements, as well as NSAIDS, heparin or digoxin, and consideration to initiate dietary potassium restriction or treatment with potassium binders, such as polysterene sulphonate resins.

Calcium channel blockers and hypokalemia

Hypokalemia during CCB treatment has been observed previously.[10-13] However, the exact mechanisms by which these drugs induce hypokalemia are not clearly established. Several possibilities have been postulated in literature. Firstly, it has been suggested that CCB therapy may influence the baro-reflex-mediated release of catecholamines which exert a shift of potassium from the extracellular to the intracellular compartment resulting in a decrease in serum potassium.[12] Secondly, studies have suggested that prolonged treatment with CCBs may result in natriuresis accompanied by a mild kaliuretic effect eventually leading to a reduction in serum potassium.[22] Thirdly, it has been proposed that CCBs may induce hypokalemia through an indirect mechanism in that they increase renal perfusion through pre-glomerular dilation which may in turn increase the kaliuretic effect of diuretics.[13] Unfortunately, the low number of patients who developed hypokalemia and were treated with both CCBs and diuretics did not allow us to verify this possibility.

In our study, the initially decreased serum potassium levels in CCB treated patients rose during prolonged follow-up. It is plausible that additional measures were put in place to manage hypokalemia such as dietary measures, potassium supplementation, or initiation of potassium sparing diuretics. Unfortunately, no data are recorded on the use of dietary measures or potassium supplementation. The use of potassium sparing diuretics was not allowed per protocol. The lack of these data precludes the verification of proper management of hypokalemia during follow-up.

Hypokalemia during follow-up was associated with an increased risk of cardiovascular events, a finding that accords with the results of the Systolic Hypertension in the Elderly Program (SHEP).[23] In the SHEP trial, chlorthalidone treatment was associated with increased incidence of hypokalemia. Furthermore, hypokalemia was significantly associated with an increased risk of cardiovascular events and only patients who remained normokalemic experienced cardiovascular benefit with chlorthalidone. Regular monitoring of serum potassium is therefore indicated after initiation of drugs, including CCBs, which may decrease serum potassium in order to avoid hypokalemia and its long-term adverse cardiovascular consequences.

Spurious and persistent hyperkalemia

Spurious hyperkalemia (pseudohyperkalemia) has been recognized long ago as a common problem in clinical care.[24] Multiple reasons have been described for spurious hyperkalemia such as inappropriate phlebotomy, improper sample storage or contamination with materials from another sample. As it is unlikely that subjects with a single erroneous serum potassium measurement are at increased CV risk, we classified the population in those who had persistent high serum potassium levels and those who had raised serum potassium at a single occasion (only month 3). As expected the relationship between serum potassium $\geq$ 5.0 mmol/L and CV risk was particularly marked in those with persistent high serum potassium levels. This implies an exposure-risk relationship and indicates that confirmed hyperkalemia requires particular attention and proper follow-up. Similar results were observed for hypokalemia although the

CV risk associated with persistent hypokalemia was not statistically significant, likely owing to a small number of events.

Limitations

Our study has some limitations. First, this is a post-hoc analysis and the associations we observed can only be interpreted as hypothesis generating. We have minimized confounding by adjusting for important clinical effect variables both at baseline and follow-up, although residual confounding can never be excluded. Second, both the RENAAL and IDNT trials were not specifically designed to investigate the effect of management of hypokalemia or hyperkalemia on cardiovascular outcomes. Therefore, no records are available how patients with hypokalemia or hyperkalemia were managed (e.g. dietary advice, potassium supplements, or potassium resins) and we were not able to verify how hypokalemia or hyperkalemia was managed during follow-up. Finally, although both trials included a broad range of patients with type 2 diabetes and nephropathy, the findings cannot be extrapolated to other populations..

Conclusions

Treatment with ARBs increases serum potassium while treatment with CCBs causes an initial decline in serum potassium. The short-term change in serum potassium, leading to hypo- and hyperkalemia, is associated with an increased risk of cardiovascular outcomes in patients with type 2 diabetes and nephropathy. Whether proper management of hypokalemia and hyperkalemia reduces this increased CV risk is an important clinical question.

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References

1. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. heart outcomes prevention evaluation study investigators. Lancet. 2000 Jan 22;355:253-9.

2. Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. Lancet. 2007 Sep 8;370:829-40.

3. Desai A. Hyperkalemia associated with inhibitors of the renin-angiotensin-aldosterone system: Balancing risk and benefit. Circulation. 2008 Oct 14;118:1609-11.

4. Desai AS, Swedberg K, McMurray JJ, et al. Incidence and predictors of hyperkalemia in patients with heart failure: An analysis of the CHARM program. J Am Coll Cardiol. 2007 Nov 13;50:1959-66.

5. Cohen HW, Madhavan S, Alderman MH. High and low serum potassium associated with cardiovascular events in diuretic-treated patients. J Hypertens. 2001 Jul;19:1315-23.

6. DeFronzo RA, Sherwin RS, Felig P, Bia M. Nonuremic diabetic hyperkalemia. possible role of insulin deficiency. Arch Intern Med. 1977 Jul;137:842-3.

7. Nicolis GL, Kahn T, Sanchez A, Gabrilove JL. Glucose-induced hyperkalemia in diabetic subjects. Arch Intern Med. 1981 Jan;141:49-53.

8. Uribarri J, Oh MS, Carroll HJ. Hyperkalemia in diabetes mellitus. J Diabet Complications. 1990 Jan-Mar;4:3-7.

9. Takaichi K, Takemoto F, Ubara Y, Mori Y. Analysis of factors causing hyperkalemia. Intern Med. 2007;46:823-9.

10. Pedersen OL, Mikkelsen E, Christensen NJ, Kornerup HJ, Pedersen EB. Effect of nifedipine on plasma renin, aldosterone and catecholamines in arterial hypertension. Eur J Clin Pharmacol. 1979 May 21;15:235-40.

11. Mimran A, Ribstein J. Effect of chronic nifedipine in patients inadequately controlled by a converting enzyme inhibitor and a diuretic. J Cardiovasc Pharmacol. 1985;7 Suppl 1:S92-5.

12. Mimran A, Ribstein J. Nitrendipine enhances the effect of adrenaline on serum potassium

in normal man. Br J Clin Pharmacol. 1986 Jul;22:117-8.

13. Murphy MB, Scriven AJ, Dollery CT. Role of nifedipine in treatment of hypertension. Br Med J (Clin Res Ed). 1983 Jul 23;287:257-9.

14. Mann JF, Yi QL, Sleight P, et al. Serum potassium, cardiovascular risk, and effects of an ACE inhibitor: Results of the HOPE study. Clin Nephrol. 2005 Mar;63:181-7.

15. Brenner BM, Cooper ME, de Zeeuw D, et al. The losartan renal protection study--rationale, study design and baseline characteristics of RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan). J Renin Angiotensin Aldosterone Syst. 2000 Dec;1:328-35.

16. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 Sep 20;345:861-9.

17. Rodby RA, Rohde RD, Clarke WR, et al. The irbesartan type II diabetic nephropathy trial: Study design and baseline patient characteristics. for the collaborative study group. Nephrol Dial Transplant. 2000 Apr;15:487-97.

18. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 Sep 20;345:851-60.

19. Miao Y, Dobre D, Heerspink HJ, et al. Increased serum potassium affects renal outcomes: A post hoc analysis of the reduction of endpoints in NIDDM with the angiotensin II antagonist losartan (RENAAL) trial. Diabetologia. 2011 Jan;54:44-50.

20. van Nieuwkoop C, Ijpelaar DH, Bolk JH. Treating proteinuria in a diabetic patient despite hyperkalaemia due to hyporeninaemic hypoaldosteronism. Neth J Med. 2007 Feb;65:75-7.

21. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. Clin J Am Soc Nephrol. 2010 Mar;5:531-48.

22. Zanchetti A, Leonetti G. Natriuretic effect of calcium antagonists. J Cardiovasc Pharmacol. 1985;7 Suppl 4:S33-7.

23. Franse LV, Pahor M, Di Bari M, Somes GW, Cushman WC, Applegate WB. Hypokalemia associated with diuretic use and cardiovascular events in the systolic hypertension in the

elderly program. Hypertension. 2000 May;35:1025-30.

24. Don BR, Sebastian A, Cheitlin M, Christiansen M, Schambelan M. Pseudohyperkalemia caused by fist clenching during phlebotomy. N Engl J Med. 1990 May 3;322:1290-2.

6

Moderate sodium diet potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers: A post-hoc analysis of the RENAAL and IDNT trials

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Abstract

Dietary sodium restriction has been shown to enhance the short-term response of blood pressure and albuminuria to angiotensin receptor blockers (ARBs). Whether this also enhances the long-term renal and cardiovascular protective effects of ARBs is unknown. We conducted a post-hoc analysis of the RENAAL and IDNT trials to test this hypothesis.

Patients with type 2 diabetes and nephropathy were randomized to ARB or non-Renin-Angiotensin-Aldosterone-System inhibition (non-RAASi) based antihypertensive therapy. Treatment effects on renal and cardiovascular outcomes were compared in subgroups based on on-treatment dietary sodium intake, measured as on-treatment 24-hour urinary sodium:creatinine ratio.

The study included 1177 subjects (36% of the overall RENAAL and IDNT population). ARB treatment compared with non-RAASi based therapy produced the greatest long-term effects on renal and cardiovascular events in the lowest tertile of sodium intake. Compared to placebo, the risk for renal events was reduced by 43% (95% confidence interval 16 to 61), 0% (-42 to 30) and increased by 37% (-4 to 96) in each tertile of sodium intake, respectively (p for trend <0.001). Cardiovascular events were reduced respectively by 37% (8 to 57), and increased by 2% (-27 to 43) and 25% (-11 to 75) (p for trend 0.021).

The treatment effects of ARB therapy compared with non-RAASi based therapy on renal and cardiovascular outcomes are greater in type 2 diabetic patients with nephropathy with lower than with higher dietary sodium intake. This underscores the call for action to avoid excessive sodium intake, particularly in type 2 diabetic patients who are receiving ARB therapy.

Keywords

Dietary sodium, Angiotensin receptor blockers, Type 2 diabetes, Diabetic nephropathy

Introduction

Agents intervening in the Renin-Angiotensin-Aldosterone-System (RAASi) are considered a mainstay of therapy in the prevention of end stage renal and cardiovascular disease in patients with diabetes, both in early and late stage of disease.[1-4] Despite proven efficacy of RAASi, it is known that the risk of renal and cardiovascular disease remains high in a substantial number of patients.[5] The high risk of renal and cardiovascular disease is closely linked to high residual blood pressure and albuminuria. To address this high residual risk, further reduction of blood pressure and albuminuria may be required. One of the options is to optimize the efficacy of RAASi.

Several studies have consistently demonstrated that dietary sodium restriction enhances the blood pressure and albuminuria response to angiotensin receptor blockers (ARB) in both diabetic and non-diabetic patients with chronic kidney disease.[6,7] However, these studies were short in duration and did not assess whether dietary sodium restriction potentiates the long-term effects of ARBs on hard renal or cardiovascular outcomes. In fact, some claim that dietary sodium restriction by itself may enhance the long-term risk for renal and or CV disease in diabetic patients.[8]

The purpose of the present study was to determine whether a low sodium diet, as indicated by low urinary sodium excretion, increases the efficacy of an ARB on hard renal and cardiovascular endpoints in type 2 diabetic patients with nephropathy. To this end, data of the the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials were merged and analyzed.

Methods

Study design

The RENAAL and IDNT trials were two large randomized, controlled double-blind trials investigating the efficacy of an ARB (losartan in RENAAL, irbesartan in IDNT) on renal outcomes compared to placebo (on a background of conventional therapy) in subjects with type 2 diabetes and nephropathy. In addition, the IDNT trial included a calcium channel blocker (amlodipine) treatment arm. The rationale, study design and outcomes for these trials have been previously published.[9,10] Patients randomized to study treatment were stepwise up titrated in two periods of 4 weeks to achieve blood pressure target of at least 135/85 mmHg (50 to 100 mg losartan (RENAAL), 75 to 300 mg irbesartan (IDNT), or 2.5 to 10 mg amlodipine (IDNT)). After the end of the titration period, the dose of other antihypertensive drugs was increased or additional antihypertensive agents (but not angiotensin converting enzyme inhibitors (ACEis) or ARBs in RENAAL and ACEis, ARBs, or calcium channel blockers in IDNT) were added to achieve the target blood pressure.

Study participants

A total of 3228 adult patients with type 2 diabetes and nephropathy participated in the RENAAL and IDNT trials. Of these participants, 1177 (591 RENAAL participants and 586 IDNT participants) collected a 24-hour urine which allowed adequate assessment of daily sodium excretion rate. These 1177 subjects were included in the current analysis. Inclusion criteria were similar but there were minor differences in detail for these trials. Patients eligible had type 2 diabetes, aged between 30-70 years and had serum creatinine levels ranging between 1.3 and 3.0 mg/dL in the RENAAL trial (with a lower limit of 1.5 mg/dL for males) and 1.0 and 3.0 mg/dL in the IDNT trial (with a lower limit of 1.2 mg/dL for males). All subjects had proteinuria, defined as 24-hour urinary protein excretion >500mg/day in the RENAAL trial and >900mg/day in the IDNT trial. Exclusion criteria for both trials were type 1 diabetes or non-diabetic renal disease.

Follow-up and assessments

After the randomization visit, subjects were seen at 4 weeks intervals until 3 months, and subsequently at 3 months intervals. Serum creatinine and electrolyte levels were measured throughout follow-up. 24-hour urinary albumin, creatinine, and sodium were measured at the randomization visit and every 6 months thereafter. The abbreviated Modification of Diet in Renal Disease (MDRD) equation was used to estimate GFR.[11] Dietary advice during the trial was in keeping with those of the American Diabetes Association. Treatment effects were calculated on renal and cardiovascular outcomes according to tertiles of the mean sodium intake during follow-up. We selected the mean sodium intake during follow-up since it more accurately reflects the exposure of a subject to a certain sodium load during the trial than a single measure. Incontinence and erroneous 24-hour urine collections are typically common in patients with diabetes as a result of diabetic neuropathy including diabetic bladder dysfunction

and poor bladder emptying.[12] To normalize for possible urine collection errors and body size dimensions we divided urinary sodium excretion by urinary creatinine excretion.[13,14] Albuminuria excretion was also normalized for urinary creatinine excretion. To establish the robustness of the analyses, we also performed all analyses according to another measure of sodium intake namely 24-hour urinary sodium excretion.

Renal and cardiovascular outcomes

The renal outcome in this analysis was defined as a composite of a confirmed doubling of serum creatinine (DSCR) from baseline or end stage renal disease (ESRD). The latter was defined as the need for chronic dialysis or renal transplantation. An additional definition for ESRD of a serum creatinine ≥ 6mg/dL (≥ 530 μmol/L) applied in the IDNT trial. The rate of estimated GFR decline over time was an additional outcome in both trials. The cardiovascular outcome was the original secondary outcome of both trials defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure or revascularization procedures. Since both the RENAAL and IDNT trial showed that ARB treatment reduces the rate of hospitalization for heart failure, the interaction between urinary sodium excretion and ARB treatment was assessed on this endpoint as well. All clinical endpoints were adjudicated by a blinded end point committee using rigorous guideline definitions.

Statistics

The risk estimates for renal and cardiovascular outcomes associated with urinary sodium excretion were estimated from Cox regression models after adjustment for potentially confounding covariates including age, gender, race, systolic and diastolic blood pressure, hemoglobin, eGFR, albumin, and albuminuria. The effects of ARB treatment versus non-RAASi based therapy on renal and cardiovascular endpoints were estimated from unadjusted Cox proportional hazard models. Test for trends in treatment effects across tertiles of urinary sodium:creatinine ratio were performed by adding interaction terms to the relevant Cox models. For subjects who experienced more than one renal or cardiovascular event during follow-up, survival time to the first relevant endpoint was used in each analysis. Participants were censored at their date of death or, for those still alive at the end of follow-up, the date of their last clinic visit before the termination of the trials. The rate of eGFR decline over time was estimated in each tertile of urinary sodium:creatinine ratio. The difference in eGFR decline between ARB and non-RAASi based therapy was estimated by a linear mixed effects model with random intercepts and random slopes. For the purpose of analysis we combined the calcium channel blocker allocated subjects with the placebo group of both trials. To ascertain the validity of this approach a sensitivity analysis was conducted excluding the patients assigned to the calcium channel blocker arm in the IDNT trial. Differences in characteristics of participating subjects among tertiles of urinary sodium:creatinine ratio were determined with one-way analysis of variance or Kruskal Wallis where appropriate. Relative risk reductions are described in the text as percentage reductions ([1 – hazard ratio] × 100). Differences between randomized groups

in blood pressure and albuminuria at month 6 were estimated by analysis of covariance. All p-values were calculated from two-tailed tests with a type I error rate of 0.05. Analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, NC, USA).

Table 1: Characteristics of the overall population and stratified according to tertiles of sodium:creatinine ratio

Variable	Overall	Stratified by sodium:creatinine ratio		
Tertiles		1	2	3
Sodium intake range*		<121	121 - 153	≥ 153
N	1177	392	393	392
Age (years)	59 (8)	58.6 (8.0)	59.8 (7.8)	59.1 (8.0)
Gender (% female)	408 (34.7)	82 (20.9)	142 (36.1)	182 (46.9)†
Race (n, %)				
White	579 (49.2)	168 (42.8)	197 (50.1)	214 (54.6)†
Black	293 (24.9)	145 (37.0)	98 (24.9)	50 (12.8)†
Hispanic	240 (20.4)	62 (15.8)	76 (19.3)	102 (26.0)†
Asian	46 (3.9)	13 (3.3)	14 (3.6)	19 (4.9)
Other	19 (1.6)	4 (1.0)	8 (2.0)	7 (1.8)
Systolic BP (mmHg)	155 (21)	153.1 (21)	155.7 (20)	156.0 (21)
Diastolic BP (mmHg)	84 (11)	84.2 (12)	83.2 (11)	83.4 (11)
Serum creatinine (mg/dl)	1.8 (0.5)	1.9 (0.5)	1.8 (0.5)	1.8 (0.6)
eGFR (ml/min/1.73m2)	44.0 (16)	45.6 (16.7)	44.1 (15.3)	42.2 (16.5)†
HbA1c (%)	8.5 (1.7)	8.4 (1.6)	8.4 (1.6)	8.8 (1.8)
Hemoglobin (mg/dl)	12.5 (2.0)	12.8 (1.9)	12.5 (2.0)	12.4 (1.9)†
Total cholesterol (mg/dl)	225 (57)	210 (57)	222 (52)	232 (59)
Body Mass Index (kg/m2)	31.2 (6.7)	31.0 (6.3)	31.6 (6.9)	30.9 (6.9)
Urinary albumin excretion (mg/24hr)	1897 [942 - 3815]	1824 [901 – 3806]	1765 [947- 3450]	2251 [963 – 3929]
Urinary creatinine excretion (g/24hr)	1.4 (0.6)	1.6 (0.6)	1.4 (0.6)	1.2 (0.4)†
Urinary albumin:creatinine ratio (mg/g)	1554 [775-2946]	1173 [639 – 2617]	1533 [783 – 2656]	1905† [910 – 3675]
Urinary sodium excretion (mmol/24hr)	181 (86)	152 (76)	179 (82)	209 (90)
Urinary sodium:creatinine ratio (mmol/g)	142 (69)	99 (34)	134 (39)	192 (85)†
Urinary urea excretion (g/24hr) ‡	9.8 (4.0)	10.3 (4.1)	9.6 (3.9)	9.4 (4.0)
Diuretic use (n, %)	720 (61)	233 (59.4)	225 (57.3)	262 (66.8)
β-blocker use (n, %)	190 (16)	67 (17.1)	60 (15.3)	63 (16.1)
Calcium antagonist use (n, %)	683 (58)	226 (57.7)	233 (59.3)	224 (57.1)

Abbreviations: BP, blood pressure; IQR, Inter Quartile Range

Values are expressed as mean with standard deviation. Urinary albumin excretion and urinary albumin:creatinine ratio is expressed as median with interquartile ranges.

† $p<0.05$ for tests for trends across urinary:sodium excretion tertiles

* Ranges are indicated for 24-hour sodium:creatinine ratio (mmol/g)

‡ Data are provided from subjects participating in the IDNT trial in whom urinary urea excretion was measured

Results

Characteristics of the study population

Table 1 shows the characteristics of the overall population and by tertiles of sodium:creatinine ratio. Participants included in the current report share the characteristics of the overall RENAAL and IDNT population. Mean sodium:creatinine ratio was 142 (±69) mmol/g and mean urinary sodium excretion was 181 (±86) mmol/24hr. Participants in the upper tertile of the sodium:creatinine ratio were more likely to be female, less likely to be of black ethnicity, had a higher 24-hour urinary albumin:creatinine ratio and a slightly but statistically significantly lower eGFR and hemoglobin level (table 1).

Effects of angiotensin receptor blockade on albuminuria and blood pressure by urinary sodium:creatinine ratio

ARB treatment compared with non-RAASi based antihypertensive therapy produced the greatest effects on albuminuria and systolic blood pressure in participants in the lowest tertile sodium intake ratio (table 2A). Similar results were observed when the population was stratified according to another measure of sodium intake, namely 24-hour urinary sodium excretion (table 2B).

Table 2:

A) Albumin:creatinine ratio and systolic blood pressure response to ARB therapy compared with non-RAASi based therapy at month 6 according to tertiles of urinary sodium:creatinine ratio

Urinary sodium to creatinine (mmol/g)	Response at month 6 (95% confidence interval)	
	24-hr ACR response (%)	Systolic BP response (mmHg)
<121	-44 (-55 to -30)	-5.0 (-7.0 to -1.9)
121 – 153	-16 (-32 to +3)	-4.6 (-5.5 to -0.4)
≥ 153	-21 (-35 to -2)	-3.5 (-3.7 to 1.8)

B) 24-hour albuminuria and systolic blood pressure response to ARB therapy compared with non-RAASi based therapy at month 6 according to urinary sodium excretion

Urinary sodium excretion (mmol/24hr)	Response at month 6 (95% confidence interval)	
	24-hr UAE response (%)	Systolic BP response (mmHg)
< 140	-31 (-42 to -19)	-6.9 (-10.7 to -3.1)
140 – 191	-17 (-29 to -3)	-3.7 (-7.4 to +0.1)
≥ 191	-19 (-31 to -4)	-2.9 (-6.7 to +0.9)

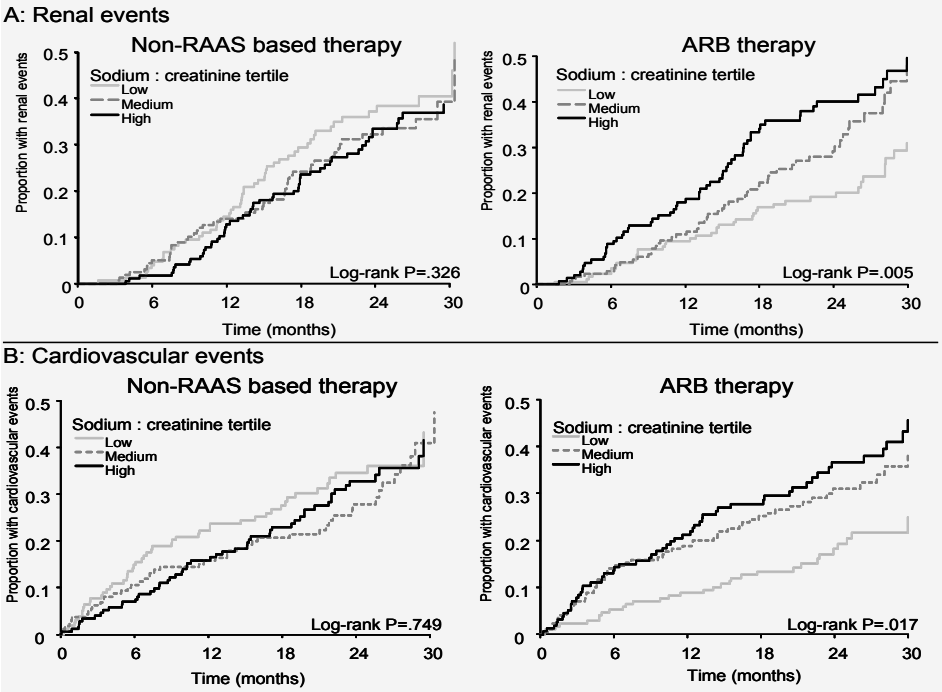

Figure 1: Kaplan Meier curves for renal (panel A) and cardiovascular (panel B) events in ARB and non-RAASi based treated subjects stratified by tertiles of sodium:creatinine ratio: <121 mmol/g; 121-153 mmol/g; ≥ 153 mmol/g.

Relationship between urinary sodium:creatinine ratio and renal and cardiovascular events

A total of 372 subjects experienced a renal event and 392 a cardiovascular event during follow-up. Figure 1 shows the Kaplan Meier survival estimates for renal and cardiovascular events in subjects treated with ARB and non-RAASi based therapy by tertiles of sodium:creatinine ratio. Sodium:creatinine ratio did not determine the renal or cardiovascular outcome of subjects in the non-RAASi based therapy group. In ARB treated subjects however, renal and cardiovascular events decreased across decreasing tertiles of sodium:creatinine ratio.

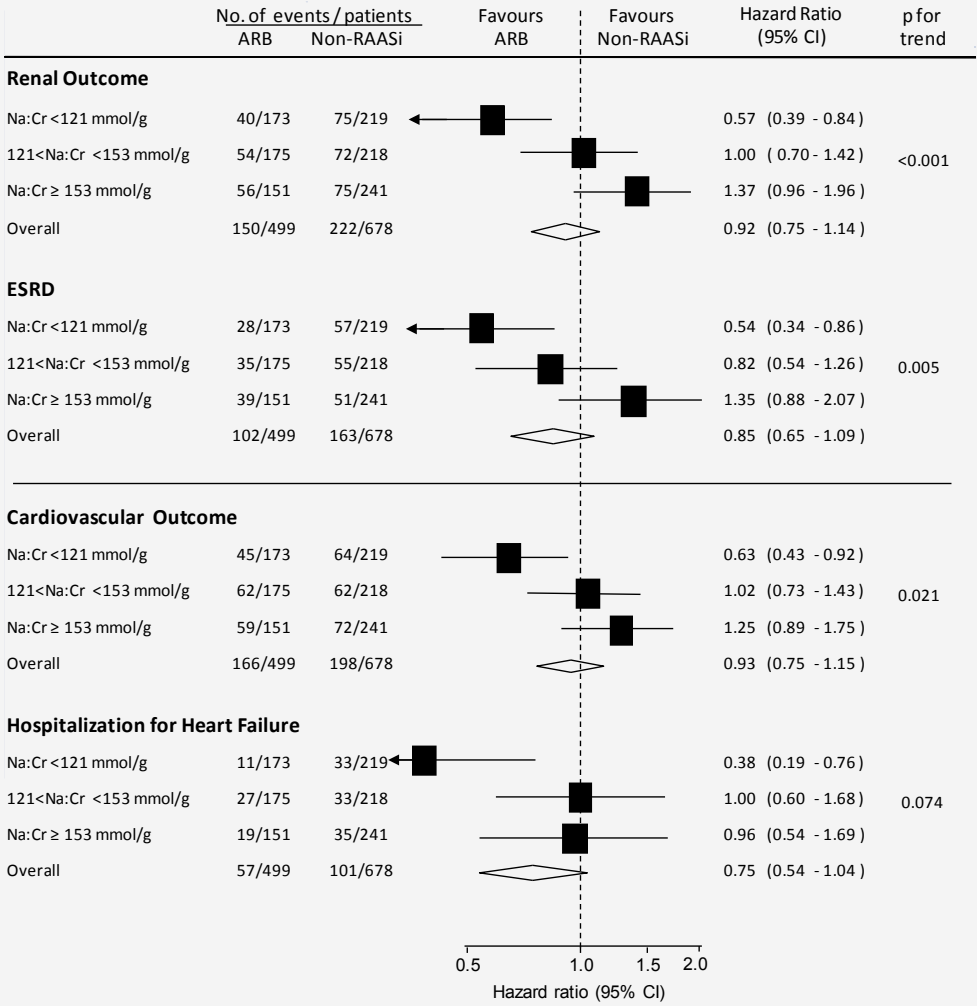

Figure 2: Effect of ARB treatment on the risk for renal and cardiovascular outcomes according to tertiles of urinary sodium:creatinine ratio. The centre of the diamond represents the overall estimate and the width its 95% confidence interval (CI). Solid boxes represent estimates of treatment effects in subgroups, and the horizontal line represents the 95% CI.

Effects of angiotensin receptor blockade on renal and cardiovascular events by urinary sodium:creatinine ratio

Compared with non-RAASi based therapy, treatment with ARBs resulted in greater relative effects on renal and cardiovascular events in subjects in the lowest tertile of sodium:creatinine ratio (p-for trend for sodium:creatinine ratio <0.001 for renal events and 0.021 for cardiovascular events; figure 2). A trend towards greater relative risk reductions for hospitalization for heart failure events was observed in participants in the lowest tertile of sodium:creatinine ratio (figure 2). An analysis that stratified the population according to 24-hour urinary sodium excretion provided nearly identical results: the relative risk reductions for renal events in the lowest versus highest tertile of 24-hour urinary sodium excretion were 25% (HR: 0.75, 95% CI: 0.53 to 1.05) versus -27% (HR: 1.27, 95% CI: 0.86 to 1.88) and for cardiovascular events 10% (HR: 0.90, 95% CI: 0.65 to 1.22), versus -3% (HR: 1.03, 95% CI: 0.73 to 1.46). An additional analysis that excluded amlodipine assigned patients in the IDNT trial provided comparable results (figure 3). Essentially similar results were obtained when the relative treatment effects were adjusted for estimated GFR or urinary urea excretion.

The effects of ARB treatment on the course of estimated GFR decline is shown in figure 4. Participants receiving ARB therapy in the lowest tertile of sodium:creatinine ratio had a significantly slower rate of renal function decline compared with non-RAASi treatment: 4.4 (95%CI 3.6 to 5.1) vs. 5.7 (5.0 to 6.4) ml/min/1.73m2; p=0.010. No difference in the rate of eGFR decline was observed between ARB and non-RAASi based therapy in the upper two tertiles of sodium:creatinine ratio (figure 4).

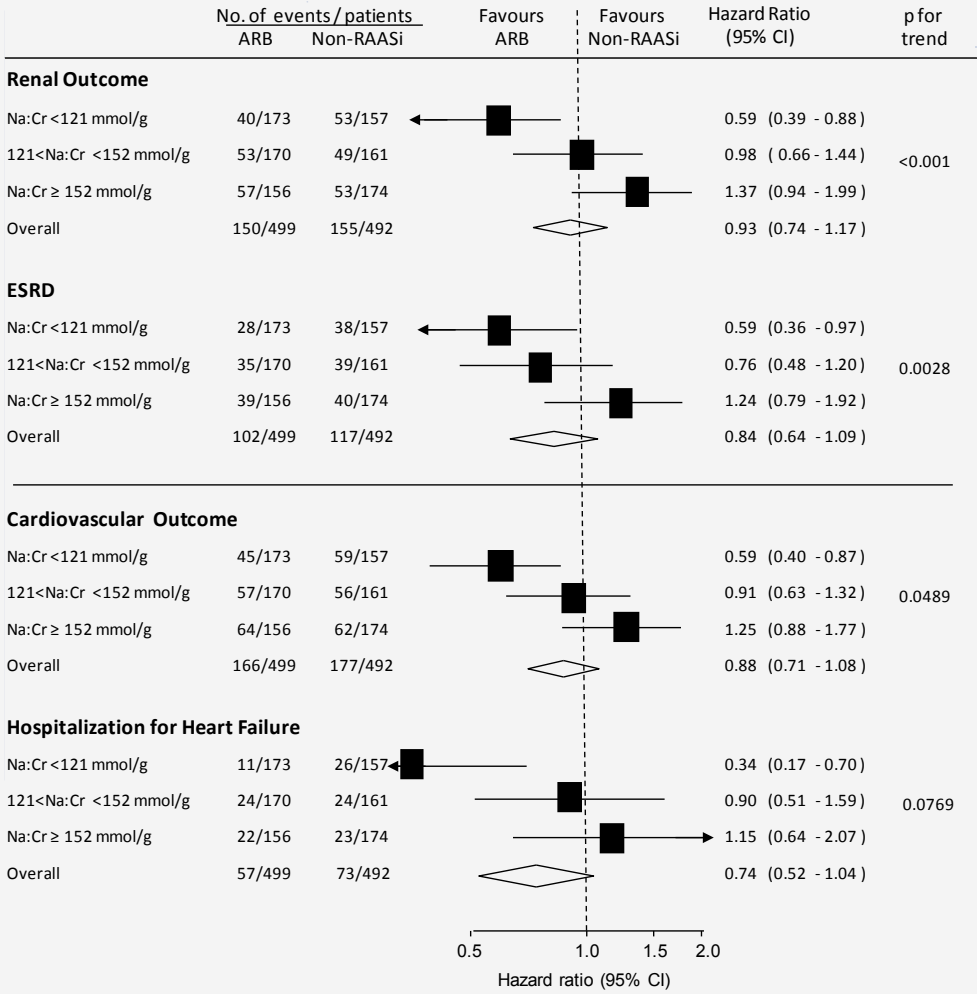

Figure 3: Effect of ARB treatment on the risk for renal outcomes in subjects according to tertiles of urinary sodium:creatinine ratio. Patients assigned to amlodipine in the IDNT trial are excluded. The centre of the diamond represents the overall estimate and the width its 95% confidence interval (CI). Solid boxes represent estimates of treatment effects in subgroups, and the horizontal line represents the 95% CI.

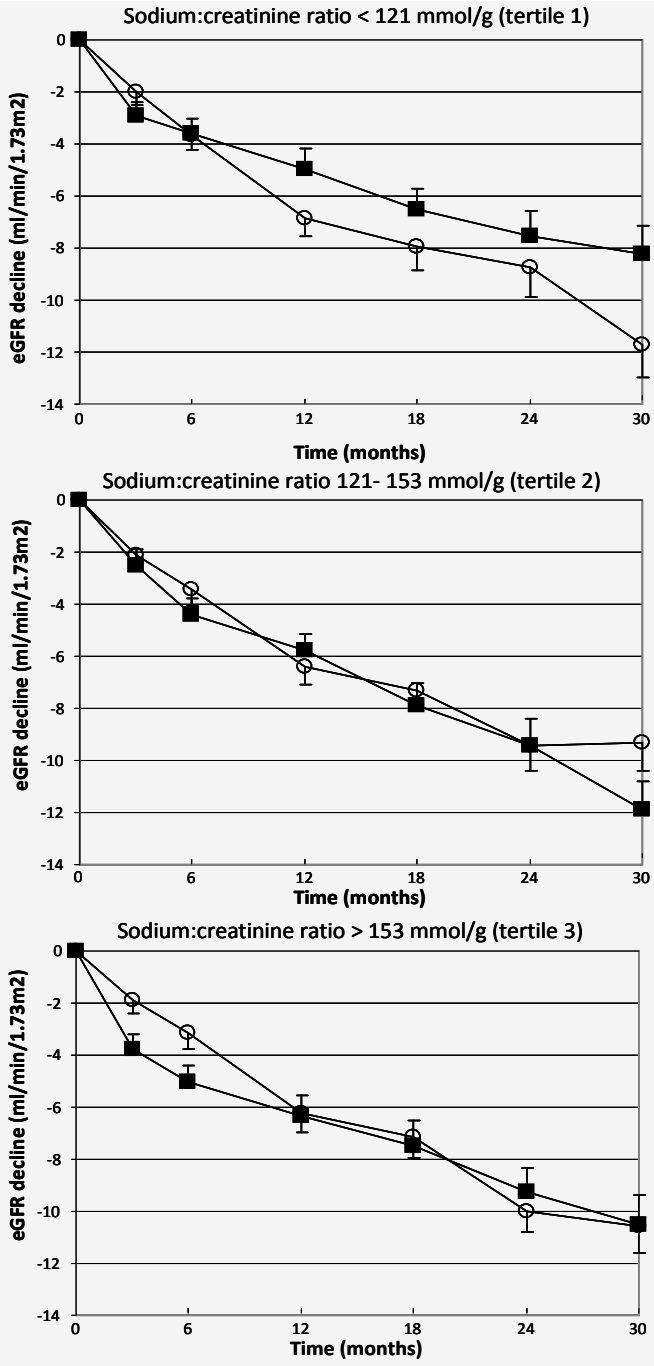

Figure 4: Mean eGFR levels through 30 months among patients who were assigned to receive ARB or non-RAASi based therapy by tertiles of sodium:creatinine ratio.

Discussion

The results of this study demonstrate that the reductions in relative risk of renal and cardiovascular events achieved with ARB therapy in type 2 diabetic patients with nephropathy are larger among subjects with lower dietary sodium intake (estimated from urinary sodium excretion). The renal and cardiovascular protective effects of ARB therapy compared with non-RAASi based therapy attenuated in subjects who ate larger amount of sodium so that in subjects with the highest sodium intake the treatment effects on hard renal and cardiovascular outcomes were completely annihilated.

Treatment guidelines for patients with chronic disease recommend dietary salt intake of less than 5 to 6 g/day which approximately equals to less than 100 mmol of sodium excretion per day.[15,16] Unfortunately, a dietary sodium intake of 5 to 6 g/day appears difficult to achieve. In our cohort average sodium excretion was 142 mmol per gram creatinine or 181 mmol/day which equals a sodium intake of approximately 11 g/day, well above the recommended limit. Similar values were reported in other large intervention trials such as the REIN I and II cohorts (approximately 170 mmol/day and 200 mmol/day), and the AASK trial (150 mmol/day).[17-19] Interestingly, the greater treatment effects in subjects within the lowest tertile of dietary sodium intake were already observed in subjects who had a liberal sodium intake of 99 mmol per gram creatinine, equivalent to 152 mmol of sodium per day, or 8.8 gram of salt per day. These data support the clinical applicability of our findings and underscore global efforts to avoid excessively high sodium intake. The data on a direct relationship, irrespective of drug treatment, between dietary sodium intake and morbidity and mortality are limited and inconclusive. A Finnish study in the general population demonstrated that a high salt intake (judged by urinary sodium excretion) significantly increased the risk of coronary heart disease mortality, cardiovascular disease mortality, and all-cause mortality.[20] In addition, long-term follow-up data from the Trials of Hypertension Prevention (TOHP) reported that subjects allocated to dietary sodium arm experienced a 25% lower risk on cardiovascular events during 10 to 15 years of follow-up.[21] Another study recently reported that renal function decline was slower among women with low than with high dietary sodium intake.[22] In contrast, Ekinci recently reported that lower sodium intake was independently associated with a higher risk for cardiovascular and all-cause mortality in individuals with type 2 diabetes.[8] However, this study should be interpreted with caution since the observational nature of the study, prone to unmeasured and residual confounding may have elicited these paradoxical results. Furthermore, the population may not be representative as high blood pressure in this population was also paradoxically associated with a decreased risk for mortality. Nonetheless, another recent population based cohort study reported that low dietary sodium intake was associated with increased risk for cardiovascular mortality.[23] Our data did not reveal any association between measures of dietary sodium intake and renal or cardiovascular outcome in non-RAASi treated individuals. The varying results on the association between dietary sodium intake and hard outcomes are probably best explained by the observational nature of all of these studies, including our study, and the different methodologies to estimate dietary sodium intake (i.e.

dietary recall as opposed to urinary sodium excretion and single versus multiple urinary sodium measurements). This may have led to unmeasured confounding and different effects of various populations with different dietary patterns. Thus, although various studies attempt to delineate the relationship between changes in salt intake and clinical outcomes they should be interpreted as hypothesis generating. Randomized controlled trials are needed to truly assess the impact of salt reduction on morbidity and mortality.

Far better are the short-term studies on the impact of restricting dietary sodium intake on blood pressure and albuminuria responses during RAASi.[6,7] No long-term hard outcome data are however available on the effects of RAASi during a low salt diet in diabetic patients. A recent post-hoc analysis of the REIN I and II trials in 500 subjects with non-diabetic nephropathy demonstrated a 3-fold larger reduction in the risk of ESRD during ramipril therapy in those with low compared with high urinary sodium excretion.[24] However, analyses from the REIN cohorts solely included patients receiving ramipril. Importantly, no correction could be made for placebo effects, rendering it impossible to correct for the fact that there might be a reason why some people ate more or less salt. By contrast, in the current study the effects of ARB treatment on renal and cardiovascular events were based on non-RAASi based controlled comparisons. In addition, the REIN data can only be applied to individuals with non-diabetic nephropathies. Due to differences in aetiology between diabetic and non-diabetic renal diseases it is uncertain whether these findings could be generalized to the broader population of patients with diabetes. Our study suggests that a liberal guideline recommended dietary sodium intake during RAAS blockade is beneficial for the rapidly growing population of people with type 2 diabetes and nephropathy. Finally, the present study suggests for the first time that a lower dietary sodium intake is associated with larger cardiovascular protective effects of ARBs.

The enhanced treatment effects on albuminuria and systolic blood pressure we observed in the lowest tertile of sodium:creatinine ratio are indicators of long-term renal and cardiovascular protection. These effects are in line with previous studies on the impact of dietary sodium intake and support the interpretation that a lower dietary sodium intake, rather than other patient characteristics, potentiate the treatment effects of ARBs.[6,8,25] Furthermore, in the lowest tertile of the sodium:creatinine ratio, ARB therapy caused an initial fall in eGFR followed by a markedly slower long-term eGFR decline compared with non-RAASi based therapy. An initial fall in GFR during ARB treatment in combination with a low sodium diet has been observed in previous studies as well.[7,26] The fall is likely of hemodynamic origin owing to a reduction in intra-glomerular pressure.[27] As an increase in intra-glomerular pressure is associated with progressive renal function loss,[28] the initial fall in eGFR can be interpreted as a sign of the therapeutic effectiveness to achieve long-term protection.[29]

Several pathophysiological mechanisms are described that may explain the blunted treatment effect of ARBs in subjects with high dietary sodium intake. Experimental and human studies have shown that a high sodium intake increases ACE activity in renal and vascular tissues, despite decreased plasma renin and angiotensinogen concentrations, which in turn attenuates the effect of ACE-inhibition at a tissue level.[30-32] In addition, high sodium intake exerts direct

harmful effects on renal tissues through activation of TGF-β.[33] Moreover, recent studies support a role of Rac-1, a transducer of cellular membrane receptor signaling, which can activate the mineralocorticoid receptor through an aldosterone independent mechanism during high salt conditions resulting in renal injury.[34] Hence, each of these deleterious effects may individually or combined offset the protective effects of RAAS inhibition during salt loading.

What could be the implications of our study? Our study demonstrates that the renal and cardiovascular protective effects of ARBs are blunted in subjects with type 2 diabetes and nephropathy in whom dietary sodium intake is excessive high. This begs for a prospective randomized controlled trial to definitively proof that restricting dietary sodium diet as adjunct to RAAS blockade improves renal and cardiovascular outcomes in chronic kidney disease. Until further data are available, we advocate avoiding high dietary sodium intake and recommend adherence to the guideline recommended target of salt intake of 5 to 6 g/day. To achieve such a change in salt intake, a concert effort of policy makers, physicians, and patients is required. In this respect, self-management is an important tool to stimulate patients to change their dietary sodium intake. Proper education directed to the individual needs of the patient, self-monitoring of dietary intake, and engaging social support from relatives have been shown to be useful to help make and maintain changes in dietary intake.[35]

The current report is a retrospective analysis of randomized controlled trial data. The results can therefore only be interpreted as hypothesis generating and not testing. It could be possible that the differences in patient's characteristics across tertiles of dietary sodium intake have contributed to the enhanced effects of ARBs in the lower tertile of urinary sodium excretion. However, the greater treatment effects in patients within the lowest tertile of sodium:creatinine ratio persisted in various sensitivity analyses such those adjusting for baseline eGFR or urinary urea excretion. Further, similar results were observed in analyses excluding subjects allocated to CCB treatment in the IDNT trial. We therefore consider it less likely that other patient characteristics have contributed to the greater renal and cardioprotective effect during a liberal sodium diet. Secondly, urinary sodium information was available for approximately one-third of the overall RENAAL and IDNT population which may have influenced the precision of the estimates of the effect sizes. It should be reminded that the RENAAL and IDNT trials were protocol driven studies and the results can only be applied to patients who share the characteristics of these populations.

Conclusions

We demonstrated that the renoprotective and cardioprotective effect conferred by angiotensin receptor blockers (losartan or irbesartan) are greater during a concomitant lower than higher sodium diet, estimated from urinary sodium excretion, in type 2 diabetic patients with nephropathy. These enhanced effects underline recent calls for population-wide intervention to reduce dietary salt intake, particularly in patients with diabetes and nephropathy treated with angiotensin receptor blockers.

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References

1. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 09/20;345:861-9.

2. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 09/20;345:851-60.

3. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001 Sep 20;345:870-8.

4. Lambers Heerspink HJ, Ninomiya T, Perkovic V. Effect of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. European heart journal. 2011 May.

5. de Zeeuw D, Heerspink HJ, Gansevoort RJ, Bakker JL. How to improve renal outcome in diabetes and hypertension - the importance of early screening for and treatment of microalbuminuria. Europ Nephrol. 2009:13.

6. Ekinci EI, Thomas G, Thomas D, et al. Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with type 2 diabetes are modulated by habitual dietary salt intake. Diabetes Care. 2009 Aug;32:1398-403.

7. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. J Am Soc Nephrol. 2008 May;19:999-1007.

8. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. Diabetes Care. 2011 Mar;34:703-9.

9. Brenner BM, Cooper ME, de Zeeuw D, et al. The losartan renal protection study--rationale, study design and baseline characteristics of RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan). J Renin Angiotensin Aldosterone Syst. 2000 Dec;1:328-35.

10. Rodby RA, Rohde RD, Clarke WR, et al. The irbesartan type II diabetic nephropathy trial: Study design and baseline patient characteristics. for the collaborative study group.

Nephrol Dial Transplant. 2000 Apr;15:487-97.

11. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. modification of diet in renal disease study group. Ann Intern Med. 1999 03/16;130:461-70.

12. Daneshgari F, Liu G, Birder L, Hanna-Mitchell AT, Chacko S. Diabetic bladder dysfunction: Current translational knowledge. J Urol. 2009 Dec;182:S18-26.

13. Flack JM, Grimm RH,Jr, Staffileno BA, et al. New salt-sensitivity metrics: Variability-adjusted blood pressure change and the urinary sodium-to-creatinine ratio. Ethn Dis. 2002 Winter;12:10-9.

14. Willett W., Stampfer M. Implications of total energy intake for epidemiologic analysis. nutritional epidemiology. New York: Oxford University Press. 1998:273-301.

15. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004 May;43:S1-290.

16. American Diabetes Association. Standards of medical care in diabetes--2011. Diabetes Care. 2011 Jan;34 Suppl 1:S11-61.

17. Norris K, Bourgoigne J, Gassman J, et al. Cardiovascular outcomes in the african american study of kidney disease and hypertension (AASK) trial. Am J Kidney Dis. 2006 Nov;48:739-51.

18. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. the GISEN group (gruppo italiano di studi epidemiologici in nefrologia). Lancet. 1997 06/28;349:1857-63.

19. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet. 1999 Jul 31;354:359-64.

20. Tuomilehto J, Jousilahti P, Rastenyte D, et al. Urinary sodium excretion and cardiovascular mortality in finland: A prospective study. Lancet. 2001 Mar 17;357:848-51.

21. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: Observational follow-up of the trials of hypertension

prevention (TOHP). BMJ. 2007 Apr 28;334:885-8.

22. Lin J, Hu FB, Curhan GC. Associations of diet with albuminuria and kidney function decline. Clin J Am Soc Nephrol. 2010 May;5:836-43.

23. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA. 2011 May 4;305:1777-85.

24. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibitioin and progression to ESRD: An outcome analysis of five-hyndred REIN and REIN-2 patients with proteinuric chronic nephropathy. American Society of Nephrology, Denver. 2010 November.

25. Slagman MCJ, Waanders F, Hemmelder MC, Lambers Heerspink HJ, Navis G, Laverman GD. Dietary sodium restriction is superior to dual blockade in enhancing the antiproteinuric and antihypertensive effect of RAAS blockade. November. 2010.

26. Houlihan CA, Allen TJ, Baxter AL, et al. A low-sodium diet potentiates the effects of losartan in type 2 diabetes. Diabetes Care. 2002 Apr;25:663-71.

27. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Arch Intern Med. 2000 03/13;160:685-93.

28. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. J Clin Invest. 1985 Aug;76:612-9.

29. Holtkamp FA, de Zeeuw D, Thomas MC, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int. 2011 Mar 30.

30. Krikken JA, Laverman GD, Navis G. Benefits of dietary sodium restriction in the management of chronic kidney disease. Curr Opin Nephrol Hypertens. 2009 Nov;18:531-8.

31. Kocks MJ, Gschwend S, de Zeeuw D, Navis G, Buikema H. Low sodium modifies the vascular effects of angiotensin-converting enzyme inhibitor therapy in healthy rats. J Pharmacol Exp Ther. 2004 Sep;310:1183-9.

32. Kobori H, Nishiyama A, Abe Y, Navar LG. Enhancement of intrarenal angiotensinogen in dahl salt-sensitive rats on high salt diet. Hypertension. 2003 Mar;41:592-7.

33. Ying WZ, Sanders PW. Dietary salt modulates renal production of transforming growth factor-beta in rats. Am J Physiol. 1998 Apr;274:F635-41.

34. Shibata S, Nagase M, Yoshida S, et al. Modification of mineralocorticoid receptor function by Rac1 GTPase: Implication in proteinuric kidney disease. Nat Med. 2008 Dec;14:1370-6.

35. Mccann BS, Bovberg BE. Promoting dietary change, in SAS, EBS, JKO, WLM(eds). handbook of helath behavior change(ed 2). new york, NY, springer. , 1998: 166-168.

7

Summary and general discussion

Bridging renal biomarkers to endpoint trials

This thesis evaluated predictive factors for response to antihypertensive treatment to improve individual long-term outcome in type 2 diabetic patients with nephropathy with a focus on angiotensin receptor blocker (ARB) therapy. Although therapy with agents intervening with the Renin-Angiotensin-Aldosterone-System (RAAS) are considered beneficial, and therefore a cornerstone antihypertensive therapy in reducing the renal and cardiovascular risk in type 2 diabetic patients with advanced nephropathy, there still remains a substantial residual risk for renal and cardiovascular morbidity and mortality.[1] This therapy resistance highlights the importance for improving existing RAAS blocking therapies and/or exploring new therapies. The RENAAL and IDNT trials provided a unique opportunity to explore to what extent early success or failure of angiotensin receptor blocker therapy could predict long-term outcome.[2,3] Both trials included essentially similar patients and monitored several potential therapy markers during follow-up which could be connected to both renal and cardiovascular endpoints.[4,5]

Important renal biomarkers on top of traditional cardiovascular biomarkers

Chapter two provided an overview on the performance of albuminuria and eGFR as biomarkers for renal and cardiovascular disease and described the effect of RAAS blockade on these risk markers in relation with long-term renal and cardiovascular outcomes. We discussed that these renal biomarkers predict renal and cardiovascular complications in patients with diabetes beyond the set of traditional cardiovascular biomarkers. Furthermore, the currently described concept gives evidence for an independent predictive value of GFR also in the absence of albuminuria. It alters the traditional paradigm describing albuminuria and eGFR as serial manifestations of kidney disease whereby albuminuria always precedes the decline in GFR. The independent additive value of albuminuria and eGFR supports guideline recommendations advocating the regular measurement of both albuminuria and eGFR to early identify patients at risk for renal and cardiovascular complications.[6]. Another important question discussed in this chapter is whether we can lower this risk by changing these renal biomarkers through pharmacological (or other) interventions. The short-term treatment induced changes in albuminuria and eGFR indeed correlates with long-term changes in renal and cardiovascular risk in such a way that a short-term reduction in albuminuria and eGFR is associated with long-term renal and cardiovascular protection.

Usefulness of albuminuria for optimal ARB treatment

Current guidelines recommend titrating ACEi and ARBs towards the maximum blood pressure lowering dose.[7] It is generally assumed that such a blood pressure driven treatment strategy is paralleled by a reduction in albuminuria, another independent risk factor for cardiovascular disease as discussed above. However, in chapter three, we demonstrated that both blood pressure and albuminuria responses may vary between individuals, and that within an individual a response in blood pressure is not always accompanied by a response in albuminuria, and vice versa. Based on this disparity in response between and within individuals, many patients do

not achieve reduction in albuminuria despite a sufficient reduction in systolic blood pressure. The magnitude of the initial treatment induced reduction in albuminuria is also independently associated with the magnitude of long-term cardiovascular risk protection. This indicates that titrating the effect of an ARB only on blood pressure may not be the optimal strategy to confer maximal cardiovascular protection. In this chapter we also showed that the combination of a low residual systolic blood pressure and a low residual albuminuria leads to optimal cardiovascular risk protection. Furthermore, it was shown that patients who achieve optimal blood pressure goal and do not have a sufficient albuminuria response consequently remain at higher cardiovascular risk. Thus, treatment in patients with type 2 diabetes should be focussed on both of these risk factors for renal and cardiovascular disease.

Initial fall in eGFR after start of ARB treatment

As we discussed, GFR is considered a renal biomarker reflecting kidney function and predicting renal and cardiovascular disease. However, RAAS inhibitors may induce an initial fall in glomerular filtration rate (GFR), often considered as an adverse event of renal insufficiency.[8] In daily practice, this often raises a safety concern that will prevent clinicians from using sufficiently high doses of ACE inhibitors or ARBs or may even lead to treatment discontinuation, in particular in type 2 diabetes patients with already reduced kidney function.

However, some small studies have demonstrated that the magnitude of initial fall in GFR is inversely related to the long-term slope of GFR decline and reversible after termination of RAAS blockade.[9,10] These data suggest that initial fall in GFR obtained from RAAS inhibitor treatment is a hemodynamic, rather than a structural phenomenon, that may serve as an early marker of subsequent slower decline of long-term renal function. Yet, this phenomenon has never been explored in patients with type 2 diabetes. In chapter four we demonstrated for the first time in a large diabetic population that the greater the initial reduction in eGFR, the slower the rate of long-term eGFR decline. This effect appears to be independent of other renal risk markers. The pharmacological explanation may be that, instead of a safety issue, a reduction in intra-glomerular pressure is an indicator of the responsiveness to therapy, in particular in the context when albuminuria and blood pressure are reduced as well. Interestingly, in chapter six a similar observation was obtained for patients treated with an ARB and the lowest tertile of dietary sodium intake. These patients also demonstrate an initial fall in eGFR associated with a subsequent smaller slope of eGFR decline, while for a higher sodium intake this phenomenon cannot be observed. The results of these studies encourage continuing treatment despite a fall in eGFR, instead of lowering dose or even discontinuation; as long as other causes such as renal artery stenosis, diminished arterial blood volume or safety issues such as hyperkalemia have been ruled out.[8] Moreover, it is recommended to analyze and report initial and long-term eGFR decline separately in clinical trials that determine effects of antihypertensive agents on renal function.

Reconsideration on potential ARB treatment limitations

Despite the beneficial effects of RAAS inhibitors, the use of ACEi and ARBs may be limited due to the occurrence of side effects such as systemic hypotension and increase in serum potassium leading to life-threatening hyperkalemia.[11,12] It is known that hyperkalemia is associated with an increased risk of cardiovascular disease, in particular in heart failure.[13] No data were available on the issue whether the development of hyperkalemia during RAAS inhibition was also associated with an increased risk of cardiovascular events in patients with diabetes type 2 and nephropathy. This is important to know because these patients are particularly prone to develop hyperkalemia during this treatment.[14-17] In chapter five we demonstrated that in patients with diabetic nephropathy ARB therapy increases serum potassium levels and that this in turn is associated with an increased risk of cardiovascular events. This must of course be interpreted in the context of the cardiovascular benefits afforded by ARB treatment. It will require further studies to establish whether careful monitoring and prevention of hyperkalemia does indeed enhance the cardioprotective effects of ARBs. We do think, however, that even small increases in serum potassium during ARB therapy could be a signal to initiate appropriate measures and therefore act as a reminder to be vigilant. Conversely, we did also find that use of calcium channel blockers in these types of patients may induce initial hypokalemia and that this hypokalemia is also associated with an increased cardiovascular risk. Thus, monitoring and correction of serum potassium may also be relevant for this class of antihypertensive agents after initiation of treatment.

Dietary sodium restriction to potentiate RAAS blocking efficacy

Another interesting approach to improve long-term outcome of RAAS inhibition is to modify factors that are associated with its response. In this respect dietary sodium intake is an important modifiable factor that mediates the efficacy of ARB therapy. Many patients with type 2 diabetes and nephropathy show poor life style behaviour such as a lack of physical activity and excessive intake of fat, sugar and sodium; habits which are potentially modifiable.[18] With respect to the latter, several small studies have demonstrated that dietary sodium restriction enhances the blood pressure and albuminuria response to RAAS inhibition.[19,20] In chapter six, we confirmed that a moderately lower dietary sodium intake indeed enhances the efficacy of ARBs to reduce blood pressure and albuminuria. Moreover, we showed that this translates into a greater risk reduction on long-term hard renal and cardiovascular outcomes. Based on these data it is advocated to avoid high dietary sodium intake and to recommend a daily salt intake of 5 to 6 g/day when ARB treatment is given to patients with diabetes and nephropathy.[21] This will require a concerted effort of physicians, patients, and policy makers as a reduced dietary intake of sodium is difficult to achieve and maintain.

Conclusions and future perspectives

In this thesis, we provided several options to predict and improve outcome of RAAS inhibition with ARBs in individual patients with type 2 diabetes mellitus and signs of nephropathy. These

options can be used for early intervention in the course of the disease in order to reach optimal benefit in terms of long-term outcome. Several important messages may be derived from the studies that we evaluated and discussed. First of all, albuminuria is an important biomarker to be reduced together with high blood pressure for achieving optimal cardiovascular protection. Several studies are ongoing to further study this approach. For example, the direct renin inhibitor aliskiren, which has demonstrated a reduction in albuminuria, is currently investigated in the ALTITUDE outcome trial.[22] Second, when a reduction in eGFR occurs after initiation of ARB treatment, without any other explanation, this should not automatically lead to dose reduction or even discontinuation of RAAS treatment. Instead, careful uptitration of the dose should be considered to achieve best outcome when other causes have been excluded. Third, maintaining potassium levels within normal levels by means of sufficient monitoring and management, in particular during initiation of therapy, may provide an opportunity to achieve the best cardiovascular protection. Finally, renal and cardiovascular protection by RAAS inhibition may be enhanced by a lower sodium intake. It should be realized that above studies are all retrospective studies that should primarily be considered as hypothesis generating. Therefore, these data still need confirmation in future, prospective trials.

Other approaches, in addition to individualized improvement of RAAS based therapy, are also necessary to reduce the high residual risk for renal and cardiovascular outcomes for these patients. Tremendous effort has been made to further improve treatment options for patients with diabetes and nephropathy. Drugs from other classes than RAAS inhibitors are being studied. For example, a larger trial is currently ongoing with atrasentan, an endothelin antagonist which has been shown to reduce albuminuria (RADAR; www.clinicaltrials.gov/show/NCT01356849).[23] Bardoxolone, a Nrf2 antagonist has shown a positive effect on glomerular filtration rate and an outcome trial is currently also ongoing (BEACON trial, www.clinicaltrials.gov/show/NCT01351675).[24] Pentoxifylline may confer renoprotection as well and long-term efficacy is currently investigated.[25] Finally, the VITAL trial, testing the selective vitamin D receptor activator paricalcitol, has shown a 20% albuminuria reduction and an initial fall in eGFR which also indicates renoprotective possibilities of this drug.[26]

However, until the value of these approaches has been established, treatment with angiotensin receptor blockers and angiotensin converting enzyme inhibitors remain the cornerstone antihypertensive treatment in patients with type 2 diabetes and nephropathy. And, as shown by this thesis, there is still ample opportunity to improve the efficacy of these agents.

References

1. de Zeeuw D, Heerspink HJ, Gansevoort RJ, Bakker JL. How to improve renal outcome in diabetes and hypertension - the importance of early screening for and treatment of microalbuminuria. Europ Nephrol. 2009:13.

2. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 09/20;345:861-9.

3. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 09/20;345:851-60.

4. Brenner BM, Cooper ME, de Zeeuw D, et al. The losartan renal protection study--rationale, study design and baseline characteristics of RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan). J Renin Angiotensin Aldosterone Syst. 2000 Dec;1:328-35.

5. Rodby RA, Rohde RD, Clarke WR, et al. The irbesartan type II diabetic nephropathy trial: Study design and baseline patient characteristics. for the collaborative study group. Nephrol Dial Transplant. 2000 Apr;15:487-97.

6. Executive summary: Standards of medical care in diabetes--2010. Diabetes Care. 2010 Jan;33 Suppl 1:S4-10.

7. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003 Dec;42:1206-52.

8. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Arch Intern Med. 2000 03/13;160:685-93.

9. Apperloo AJ, de ZD, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney Int. 1997 03;51:793-7.

10. Hansen HP, Rossing P, Tarnow L, Nielsen FS, Jensen BR, Parving HH. Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. Kidney Int. 1995 06;47:1726-31.

11. Ma TK, Kam KK, Yan BP, Lam YY. Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: Current status. Br J Pharmacol. 2010 Jul;160:1273-92.

12. Turgut F, Balogun RA, Abdel-Rahman EM. Renin-angiotensin-aldosterone system blockade effects on the kidney in the elderly: Benefits and limitations. Clin J Am Soc Nephrol. 2010 Jul;5:1330-9.

13. Cohen HW, Madhavan S, Alderman MH. High and low serum potassium associated with cardiovascular events in diuretic-treated patients. J Hypertens. 2001 Jul;19:1315-23.

14. DeFronzo RA, Sherwin RS, Felig P, Bia M. Nonuremic diabetic hyperkalemia. possible role of insulin deficiency. Arch Intern Med. 1977 Jul;137:842-3.

15. Nicolis GL, Kahn T, Sanchez A, Gabrilove JL. Glucose-induced hyperkalemia in diabetic subjects. Arch Intern Med. 1981 Jan;141:49-53.

16. Takaichi K, Takemoto F, Ubara Y, Mori Y. Analysis of factors causing hyperkalemia. Intern Med. 2007;46:823-9.

17. Uribarri J, Oh MS, Carroll HJ. Hyperkalemia in diabetes mellitus. J Diabet Complications. 1990 Jan-Mar;4:3-7.

18. Reaven GM. Dietary therapy for non-insulin-dependent diabetes mellitus. N Engl J Med. 1988 Sep 29;319:862-4.

19. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. J Am Soc Nephrol. 2008 May;19:999-1007.

20. Ekinci EI, Thomas G, Thomas D, et al. Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with type 2 diabetes are modulated by habitual dietary salt intake. Diabetes Care. 2009 Aug;32:1398-403.

21. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: Executive summary. the task force on diabetes and cardiovascular diseases of the european society of cardiology (ESC) and of the european association for the study of diabetes (EASD). Eur Heart J. 2007 Jan;28:88-136.

22. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren trial in type 2 diabetes using

cardio-renal endpoints (ALTITUDE): Rationale and study design. Nephrol Dial Transplant. 2009 May;24:1663-71.

23. Kohan DE, Pritchett Y, Molitch M, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. J Am Soc Nephrol. 2011 Apr;22:763-72.

24. Pergola PE, Raskin P, Toto RD, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med. 2011 Jun 24.

25. Navarro-Gonzalez JF, Muros M, Mora-Fernandez C, Herrera H, Meneses B, Garcia J. Pentoxifylline for renoprotection in diabetic nephropathy: The PREDIAN study. rationale and basal results. J Diabetes Complications. 2010 Dec 6.

26. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): A randomised controlled trial. Lancet. 2010 Nov 6;376:1543-51.

Samenvatting en algemene discussie

Renale biomarkers relateren aan eindpunt studies

Dit proefschrift heeft onderzocht hoe individuele lange termijn effecten van bloeddrukverlagende behandeling kunnen worden voorspeld en verbeterd bij patiënten met diabetes type 2 en nierziekten. Er is gekeken hoe bepaalde indicatoren bepalend zijn voor het effect van behandeling op de korte termijn en of ze daarnaast voorspellend zijn voor het effect op de lange termijn. De focus lag daarbij op de behandeling met angiotensine receptor blokkers (ARB). Dit zijn bloeddrukverlagende middelen die ingrijpen op het the Renine Angiotensine Aldosteron Systeem (RAAS). Bloeddrukverlagende behandeling met deze middelen verminderen het lange termijn risico voor eindstadium nierfalen (renale uitkomsten) en voor complicaties van hart- en vaatziekten (cardiovasculaire morbiditeit en cardiovasculaire mortaliteit) en sterfte (mortaliteit, alle doodsoorzaken) bij patiënten met type 2 diabetes en bestaande nierziekte. Patiënten hebben echter ook gedurende behandeling met deze middelen nog steeds een aanzienlijk resterend risico op renale en cardiovasculaire complicaties (therapie resistentie).[1] Deze therapie resistentie benadrukt het belang van het verbeteren van de bestaande behandeling van RAAS blokkade en/of het ontdekken van nieuwe therapieën.

Voor het onderzoek in dit proefschrift is gebruik gemaakt van de individuele patiëntgegevens van de RENAAL en IDNT studies. Deze 2 grote internationale studies hebben een gunstig effect laten zien van ARB behandeling op lange termijn complicaties. In beide studies waren nagenoeg dezelfde patiënten geïncludeerd, en werden verscheidene biomarkers (meetbare biologische indicatoren, bijvoorbeeld bloeddruk, cholesterol, eiwit in de urine), die mogelijk gerelateerd konden worden aan renale en cardiovasculaire uitkomsten gedurende de studies, gevolgd.[2-5]

De gegevens uit deze studies boden een unieke kans om verder te onderzoeken in hoeverre het vroegtijdige succes of falen van ARB behandeling voorspellend is geweest voor renale en cardiovasculaire uitkomsten op de lange termijn.

Belangrijke renale biomarkers naast de traditionele cardiovasculaire biomarkers

Hoofdstuk 2 laat een overzicht van de voorspellende waarde van renale biomarkers albuminurie (eiwit uitscheiding in de urine) en eGFR (glomerulaire nierfiltratiesnelheid, een maat voor nierfunctie) zien voor renale en cardiovasculaire uitkomsten op de lange termijn. Vervolgens beschrijven we de effecten van ARB behandeling op deze biomarkers in relatie tot renale en cardiovasculaire uitkomsten op de lange termijn. We bespreken dat deze renale biomarkers het renale en cardiovasculaire risico kunnen voorspellen bovenop de bestaande traditionele risicofactoren voor hart- en vaatziekten in patiënten met diabetes. Daarnaast laten we zien dat de eGFR ook een onafhankelijke voorspellende waarde heeft in afwezigheid van albuminurie. Dit onderscheidt zich van het bestaande concept waarbij albuminurie en eGFR daling opeenvolgende manifestaties zijn van de nierziekte. Hierbij wordt een daling in eGFR voorafgegaan door het ontstaan van albuminurie. De onafhankelijk voorpellende waarde van albuminurie en eGFR is in overeenstemming met de richtlijnen die adviseren om zowel albuminurie als eGFR regelmatig te bepalen om patiënten met renale en cardiovasculaire complicaties tijdig

te kunnen identificeren.[6]

Daarnaast beantwoorden we de vraag of farmacologische (of andere) interventie een verandering geeft van deze renale biomarkers en deze verandering vervolgens gerelateerd is met het verminderen van het risico op complicaties op de lange termijn. De door behandeling geïnduceerde veranderingen in albuminurie en eGFR op de korte termijn waren inderdaad gerelateerd aan veranderingen in het renale en cardiovasculaire risico op de lange termijn: een verlaging van albuminuria op korte termijn was geassocieerd met nier- en cardiovasculaire bescherming op lange termijn.

De meerwaarde van albuminurie bij het optimaliseren van ARB behandeling

De huidige richtlijnen adviseren om angiotensine converting enzyme (ACE) remmers en ARBs te titreren op geleide van de maximale bloeddrukverlagende dosering.[7] Het wordt algemeen aangenomen dat deze strategie gericht op bloeddrukverlaging ook resulteert in een daling van de albuminurie (wat zoals hierboven beschreven een andere onafhankelijke risicofactor voor cardiovasculaire complicaties is). In **hoofdstuk 3** laten we echter zien dat er niet altijd een goede samenhang is tussen de mate van bloeddrukverlaging en albuminurierespons: binnen een individu loopt de bloeddrukrespons niet altijd synchroon met de albuminurierespons of andersom. Er zijn bijvoorbeeld patiënten die wel een goede bloeddrukverlaging hebben, maar geen albuminuriedaling. De mate van verandering in albuminurie is echter ook onafhankelijk gerelateerd aan het cardiovasculaire risico op de lange termijn. Dit betekent dat titratie op alleen het bloeddrukverlagende effect van een ARB mogelijk niet de optimale strategie is om maximale vermindering van albuminurie en daarmee het cardiovasculaire risico op de lange termijn te realiseren. We laten in dit hoofdstuk ook zien dat de combinatie van een lage bloeddrukwaarde en lage albuminuriewaarde door behandeling maximale cardiovasculaire bescherming biedt. Tot slot laten we zien dat patiënten met een optimaal bereikte bloeddrukverlaging maar onvoldoende verlaging in hun albuminurie toch nog een verhoogd cardiovasculair lange termijn risico hebben. Er kan daarmee geconcludeerd worden dat behandeling van patiënten met type 2 diabetes en nierziekte gericht moet zijn op zowel bloeddrukverlaging als albuminuriedaling.

Initiële daling in eGFR na start van behandeling met een ARB

Zoals besproken is eGFR (glomerulaire nierfiltratie snelheid) een renale marker die de nierfunctie weergeeft en die de kans op nierfalen en cardiovasculaire complicaties op de lange termijn kan voorspellen. ARBs kunnen echter bij de start van de behandeling een daling in eGFR veroorzaken. Deze daling wordt doorgaans beschouwd als een teken van acute nierfunctieverslechtering Dit is in de dagelijkse praktijk vaak aanleiding om een te lage dosis van ACE remmers of ARBs voor te schijven of zelfs de behandeling te stoppen, vooral bij patiënten met diabetes type 2 en een al verminderde nierfunctie.[8]

Er zijn echter een aantal kleine studies die hebben laten zien dat de mate van initiële daling van eGFR geassocieerd is met een langzamere daling van de eGFR op de langere termijn. Bovendien bleek de initiële daling omkeerbaar te zijn na het stoppen van behandeling met RAAS

blokkers.[9, 10] Deze data zouden erop kunnen wijzen dat de initiële daling in eGFR door RAAS blokkade een hemodynamisch effect van de behandeling is, en geen structurele beschadiging van de nier betreft. Daarmee kan het een vroegtijdige indicator zijn van de vervolgens langzamere afname van nierfunctie op de lange termijn. Dit fenomeen is echter nooit onderzocht in een grote groep patiënten met type 2 diabetes. In **hoofdstuk 4** laten we voor de eerste keer in een grote groep mensen met diabetes zien dat hoe groter de initiële daling in eGFR des te kleiner de daling in eGFR op de lange termijn. Dit effect was onafhankelijk van andere voorspellers van lange termijn uitkomsten op de nier. De farmacologische verklaring voor dit fenomeen kan zijn dat de vermindering van intraglomerulaire druk een teken is van therapierespons, in plaats van een teken van nierschade, vooral als naast de eGFR ook de albuminurie en de bloeddruk verlaagd worden. Het is interessant dat dit fenomeen ook gezien wordt in hoofdstuk 6 bij patiënten met beperkte zoutinname die werden behandeld met een ARB. Deze patiënten lieten ook een initiële daling in de eGFR zien gerelateerd aan een daaropvolgend kleinere daling van de lange termijn eGFR. Dit fenomeen werd niet gezien bij patiënten met een hogere zoutinname. Deze resultaten zijn daarmee een goede reden om door te gaan met behandelen in plaats van, zoals nu vaak gebeurt, de dosis te verlagen of de behandeling te stoppen. Dit alles geld alleen als andere factoren die verantwoordelijk kunnen zijn voor een acute daling in de eGFR uitgesloten zijn (bijvoorbeeld arteriestenose, verminderde arteriële bloeddoorstroming) en er geen sprake is van andere klinische problemen (zoals verhoogde kaliumconcentratie in het bloed).[8] Daarnaast adviseren we om in toekomstige klinische studies de initiële en lange termijn daling in de eGFR apart te analyseren en te rapporteren indien het effect van het bloeddrukverlagende geneesmiddel op de nierfunctie wordt onderzocht.

Heroverwegingen op mogelijke beperkingen van ARB behandeling

Ondanks de gunstige effecten van RAAS blokkade kan de toepasbaarheid van ACE remmers en ARBs beperkt worden door mogelijke bijwerkingen. Voorbeelden hiervan zijn (te) lage bloeddruk of een verhoging van de kaliumspiegel in het bloed (hyperkaliëmie), wat levensbedreigend kan zijn omdat het kan leiden tot cardiovasculaire complicaties.[11-13] De kans dat behandeling met RAAS-blokkade hyperkaliëmie veroorzaakt is groter bij patiënten met diabetes en nierziekte.[14-17] Het is echter onbekend of hyperkaliëmie door behandeling met RAAS-blokkade in deze groep patiënten een verhoogde kans geeft op cardiovasculaire complicaties.

In **hoofdstuk 5** lieten we zien dat behandeling met ARBs de kaliumspiegel bij patiënten met type 2 diabetes en nierziekte doet stijgen. Dit blijkt geassocieerd te zijn met een verhoogd risico op cardiovasculaire complicaties.

Daarnaast konden we ook laten zien dat calcium kanaal blokkers (in tegenstelling tot ARBs) soms een initiële *daling* in kalium veroorzaken. Dit bleek ook geassocieerd te zijn met een verhoogd risico op cardiovasculaire complicaties.

Deze bevindingen moeten echter geplaatst worden in de context dat ARBs - maar ook calcium kanaal blokkers - over het algemeen juist gunstige effecten hebben op hart- en vaatziekten. Uit verdere studies zal daarom moet blijken of het intensief volgen en zo nodig behandelen

van hyperkaliëmie het gunstige cardiovasculaire effect van ARBs verder kan verbeteren. Dit zal ook nog moeten blijken voor behandelen van hypokaliëmie tijdens calcium kanaal blokker gebruik. Op basis van de huidige kennis adviseren we wel dat zelfs kleine veranderingen in de kaliumspiegel tijdens behandeling met ARBs of calcium kanaal blokkers reden geven tot waakzaamheid.

Beperken van zoutinname om het effect van RAAS blokkade te versterken

Een andere interessante benadering om de effecten van RAAS blokkade met ARBs verder te verbeteren is door het aanpassingen van factoren die de respons op behandeling met ARBs beïnvloeden. Een van deze factoren die de respons op ARBs beïnvloedt is zoutinname. Een groot aantal patiënten met type 2 diabetes en nierziekte hebben een overmatige zoutinname als een van de gewoontes van een ongezonde levensstijl. Deze levensstijlfactor is echter wel te veranderen.[18]

Diverse kleine studies die hebben laten zien dat het verminderen van deze zoutinname de effectiviteit van RAAS blokkade (de bloeddrukverlaging en albuminuriedaling) kan bevorderen.[19, 20] In **hoofdstuk 6** konden we de resultaten van de eerdere kleine studies bevestigen: gematigde zoutinname tijdens ARB behandeling resulteert in een grotere bloeddrukverlaging en albuminuriedaling. Deze betere respons op behandeling met ARBs leidde tot minder renale en cardiovasculaire complicaties op de lange termijn. Daarom raden we aan om een hoge zoutinname te vermijden (streven naar een dagelijkse zoutinname van 5 tot 6 gram) indien patiënten met diabetes en nierziekte met een ARB worden behandeld.[21] Dit vraagt wel om een voortdurende inspanning van behandelaars, patiënten en beleidsmakers, omdat het bereiken en behouden van een lage zoutinname moeilijk is te realiseren.

Conclusies en toekomstperspectief

In dit proefschrift hebben we laten zien dat er diverse mogelijkheden zijn om de individuele uitkomsten op RAAS blokkade met ARBs te voorspellen en te verbeteren bij type 2 diabetes en nierziekte. Er zijn verscheidene boodschappen te herleiden uit de studies die we hebben gedaan. Ten eerste dient naast de bloeddrukverlaging de albuminuriedaling een belangrijk doel te zijn van ARB behandeling om daarmee een optimale cardiovasculaire bescherming te bereiken. Diverse studies zijn momenteel gaande om deze benadering verder te bestuderen. De directe renine blokker aliskiren, die een verlaging in albuminurie liet zien, wordt bijvoorbeeld onderzocht in de ALTITUDE lange termijn studie.[22] Ten tweede, een verlaging in eGFR als gevolg van het starten van de behandeling met een ARB, dient niet direct aanleiding te geven tot een dosisaanpassing of het stoppen van de behandeling. Tenminste, zolang andere factoren die kunnen zorgen voor een daling van de GFR uitgesloten zijn. De dosis moet juist voorzichtig worden opgetitreerd om de best mogelijke uitkomst te realiseren. Tot slot, lange termijn nierbescherming en cardiovasculaire bescherming door RAAS blokkade kan versterkt worden door een lagere zoutinname. Bovenstaande studies zijn echter wel retrospectief en zijn daarmee primair bedoeld als hypothese genererend. Deze resultaten dienen daarom nog

wel met toekomstige prospectieve studies bevestigd te worden.

Naast de mogelijkheden voor het verbeteren van de individuele RAAS blokkerende behandeling zijn er ook andere behandelingsstrategieën nodig om het risico op renale en cardiovasculaire complicaties in deze patiënten verder te verlagen. Diverse andere medicijnen worden momenteel bestudeerd. Zo is er een grote studie gaande met atrasentan, een endotheline antagonist die al een verlaging in albuminurie heeft laten zien (RADAR; www.clinicaltrials.gov/show/NCT01356849).[23] Bardoxolone, een Nrf2 antagonist liet al een gunstig effect op de glomerulaire filtratie snelheid (nierfunctie) zien en een lange termijn studie is momenteel gaande (BEACON studie; www.clinicaltrials.gov/show/NCT01351675).[24] Pentoxyfilline is een ander medicijn dat wellicht ook voor nierbescherming kan zorgen. De lange termijn effectiviteit wordt momenteel onderzocht.[25] Tot slot, de VITAL studie, die de selectieve vitamine D receptor activator paricalcitol heeft onderzocht, liet een 20% verlaging in albuminurie en een initiële daling van eGFR zien. Dit kan een aanwijzing zijn voor de nierbeschermende werking van dit middel.[26]

Maar zolang de betekenis van deze behandelingen nog niet vast staat zal de behandeling met angiotensine receptor blokkers en angiotensine converting enzyme remmers de belangrijkste bloeddrukverlagende behandeling bij patiënten met type 2 diabetes en nierziekte blijven. En zoals we hebben laten zien in dit proefschrift is er nog steeds een duidelijke verbetering van de effectiviteit van deze middelen mogelijk.

Referenties

1. de Zeeuw D, Heerspink HJ, Gansevoort RJ, Bakker JL. How to improve renal outcome in diabetes and hypertension - the importance of early screening for and treatment of microalbuminuria. Europ Nephrol. 2009:13.

2. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 09/20;345:861-9.

3. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 09/20;345:851-60.

4. Brenner BM, Cooper ME, de Zeeuw D, et al. The losartan renal protection study--rationale, study design and baseline characteristics of RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan). J Renin Angiotensin Aldosterone Syst. 2000 Dec;1:328-35.

5. Rodby RA, Rohde RD, Clarke WR, et al. The irbesartan type II diabetic nephropathy trial: Study design and baseline patient characteristics. for the collaborative study group. Nephrol Dial Transplant. 2000 Apr;15:487-97.

6. Executive summary: Standards of medical care in diabetes--2010. Diabetes Care. 2010 Jan;33 Suppl 1:S4-10.

7. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003 Dec;42:1206-52.

8. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Arch Intern Med. 2000 03/13;160:685-93.

9. Apperloo AJ, de ZD, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney Int. 1997 03;51:793-7.

10. Hansen HP, Rossing P, Tarnow L, Nielsen FS, Jensen BR, Parving HH. Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. Kidney Int. 1995 06;47:1726-31.

11. Ma TK, Kam KK, Yan BP, Lam YY. Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: Current status. Br J Pharmacol. 2010 Jul;160:1273-92.

12. Turgut F, Balogun RA, Abdel-Rahman EM. Renin-angiotensin-aldosterone system blockade effects on the kidney in the elderly: Benefits and limitations. Clin J Am Soc Nephrol. 2010 Jul;5:1330-9.

13. Cohen HW, Madhavan S, Alderman MH. High and low serum potassium associated with cardiovascular events in diuretic-treated patients. J Hypertens. 2001 Jul;19:1315-23.

14. DeFronzo RA, Sherwin RS, Felig P, Bia M. Nonuremic diabetic hyperkalemia. possible role of insulin deficiency. Arch Intern Med. 1977 Jul;137:842-3.

15. Nicolis GL, Kahn T, Sanchez A, Gabrilove JL. Glucose-induced hyperkalemia in diabetic subjects. Arch Intern Med. 1981 Jan;141:49-53.

16. Takaichi K, Takemoto F, Ubara Y, Mori Y. Analysis of factors causing hyperkalemia. Intern Med. 2007;46:823-9.

17. Uribarri J, Oh MS, Carroll HJ. Hyperkalemia in diabetes mellitus. J Diabet Complications. 1990 Jan-Mar;4:3-7.

18. Reaven GM. Dietary therapy for non-insulin-dependent diabetes mellitus. N Engl J Med. 1988 Sep 29;319:862-4.

19. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. J Am Soc Nephrol. 2008 May;19:999-1007.

20. Ekinci EI, Thomas G, Thomas D, et al. Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with type 2 diabetes are modulated by habitual dietary salt intake. Diabetes Care. 2009 Aug;32:1398-403.

21. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: Executive summary. the task force on diabetes and cardiovascular diseases of the european society of cardiology (ESC) and of the european association for the study of diabetes (EASD). Eur Heart J. 2007 Jan;28:88-136.

22. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren trial in type 2 diabetes using

cardio-renal endpoints (ALTITUDE): Rationale and study design. Nephrol Dial Transplant. 2009 May;24:1663-71.

23. Kohan DE, Pritchett Y, Molitch M, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. J Am Soc Nephrol. 2011 Apr;22:763-72.

24. Pergola PE, Raskin P, Toto RD, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med. 2011 Jun 24.

25. Navarro-Gonzalez JF, Muros M, Mora-Fernandez C, Herrera H, Meneses B, Garcia J. Pentoxifylline for renoprotection in diabetic nephropathy: The PREDIAN study. rationale and basal results. J Diabetes Complications. 2010 Dec 6.

26. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): A randomised controlled trial. Lancet. 2010 Nov 6;376:1543-51.

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